08/624,508

Copy for the Elected Office (EO/US)

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92*bis*.1 and Administrative Instructions, Section 422)

To:

SAMA, Daniele
Sama Patents
Via Masera, 10
I-20129 Milano
ITALIE

Date of mailing *(day/month/year)*: 02 April 1996 (02.04.96)	
Applicant's or agent's file reference: 94113B99	IMPORTANT NOTIFICATION
International application No.: PCT/EP94/03182	International filing date *(day/month/year)*: 23 September 1994 (23.09.94)

1. The following indications appeared on record concerning:

[X] the applicant [ ] the inventor [ ] the agent [ ] the common representative

Name and Address:

NICOX LIMITED
17 Dame Street
Dublin 2
Ireland

State of Nationality: IE
State of Residence: IE
Telephone No.:
Facsimile No.:
Teleprinter No.:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [X] the name [X] the address [ ] the nationality [ ] the residence

Name and Address:

NICOX S.A.
45 Avenue Kléber
F-75116 Paris
France

State of Nationality: FR
State of Residence: FR
Telephone No.:
Facsimile No.:
Teleprinter No.:

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[ ] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer: G. Bähr

Telephone No. (41-22) 730.91.11

Form PCT/IB/306 (July 1992)

Copy for the Elected Office (EO/ US)

[redacted]TENT COOPERATION TREA[redacted]

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92*bis*.1 and Administrative Instructions, Section 422)

To:
SAMA, Daniele
Sama Patents
Via Masera, 10
I-20129 Milano
ITALIE

Date of mailing *(day/month/year)* 24 May 1995 (24.05.95)

Applicant's or agent's file reference
94113B99

IMPORTANT NOTIFICATION

International application No.
PCT/EP94/03182

International filing date *(day/month/year)* 23 September 1994 (23.09.94)

1. The following indications appeared on record concerning:

☐ the applicant ☐ the inventor ☒ the agent ☐ the common representative

Name and Address
TRUPIANO, Roberto
Brevetti Europa S.r.l.
Piazza Bernini, 6
I-20133 Milano
ITALY

State of Nationality | State of Residence

Telephone No.

Facsimile No.

Teleprinter No.

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☒ the name ☒ the address ☐ the nationality ☐ the residence

Name and Address
SAMA, Daniele
Sama Patents
Via Masera, 10
I-20129 Milano
ITALY

State of Nationality | State of Residence

Telephone No.
2-29521908

Facsimile No.
2-29521926

Teleprinter No.

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

☒ the receiving Office
☐ the International Searching Authority
☒ the International Preliminary Examining Authority
☐ the designated Offices concerned
☒ the elected Offices concerned
☐ other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer
J. Leitao

Telephone No. (41 22) 730.91.11

Form PCT/IB/306 (July 1992)

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

United States Patent and Trademark Office
(Box PCT)
Washington D.C. 20231
United States of America

in its capacity as elected Office

Date of mailing: 24 May 1995 (24.05.95)	
International application No.: PCT/EP94/03182	Applicant's or agent's file reference: 94113B99
International filing date: 23 September 1994 (23.09.94)	Priority date: 06 October 1993 (06.10.93)
Applicant: DEL SOLDATO, Piero	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

25 April 1995 (25.04.95)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer:

J. Leitao

Telephone No.: (41-22) 730.91.11

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING DOCUMENT TRANSMITTED

To:

United States Patent and Trademark Office
(Box PCT)
Washington D.C. 20231
United States of America

in its capacity as elected Office

Date of mailing (day/month/year) 19 January 1996 (19.01.96)	
International application No. PCT/EP94/03182	**International filing date** (day/month/year) 23 September 1994 (23.09.94)
Applicant NICOX LIMITED et al	

The International Bureau transmits herewith the following documents and number thereof:

_____ copy of the international preliminary examination report and annexes (Article 36(3)(a))

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

K. Andreasson

Telephone No.: (41-22) 730.91.11

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
94113B99		
International application No.	International filing date (day/month/year)	(Earliest) Priority Date (day/month/year)
PCT/EP 94/03182	23/09/94	06/10/93
Applicant		
NICOX LIMITED et al.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. [ ] **Certain claims were found unsearchable** (see Box I).

2. [ ] **Unity of invention is lacking** (see Box II).

3. [ ] The international application contains disclosure of a **nucleotide and/or amino acid sequence listing** and the international search was carried out on the basis of the sequence listing
   - [ ] filed with the international application.
   - [ ] furnished by the applicant separately from the international application,
     - [ ] but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.
   - [ ] Transcribed by this Authority

4. With regard to the **title**,
   - [X] the text is approved as submitted by the applicant.
   - [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,
   - [X] the text is approved as submitted by the applicant.
   - [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is:
   Figure No. _____
   - [ ] as suggested by the applicant.
   - [ ] because the applicant failed to suggest a figure.
   - [ ] because this figure better characterizes the invention.
   - [ ] None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 94/03182

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07C203/04 C07D487/04 C07D209/28 A61K31/40 A61K31/405
A61K31/21 //(C07D487/04,209:00,209:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07C C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DE,A,17 93 828 (SYNTEX CORP.) 22 April 1976 see the whole document & ZA,A,6 707 597 (...) cited in the application	1-18
A	DE,A,14 43 429 (BOOTS PURE DRUG COMPANY LTD.) 24 October 1968 see the whole document & GB,A,971 700 (...) cited in the application	1-18
A	US,A,3 758 544 (SYNTEX CORP.) 11 September 1973 see abstract; claims & DE,A,19 34 460 (...) 23 June 1977 cited in the application	1-18

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
14 December 1994	- 4. 01. 95

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Paisdor, B

Form PCT/ISA/210 (second sheet) (July 1992)

International Application No
PCT/EP 94/03182

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DE,A,28 14 556 (SANKYO CO., LTD.) 12 October 1978 cited in the application see claims	1-18
P,A	WO,A,94 12463 (HCT-HEALTH CARE TRADING LTD.) 9 June 1994 see abstract; claims	1-18
P,A	WO,A,94 04484 (CORLAY S.L. & METGROVE LTD.) 3 March 1994 see abstract; claims	1-18

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 94/03182

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE-A-1793828	22-04-76	DE-A,B,C 1793825	05-02-76
		CA-A- 960689	07-01-75
		CA-A- 991655	22-06-76
		CH-A- 517690	15-01-72
		CH-A- 520644	31-03-72
		CH-A- 520645	31-03-72
		CH-A- 537369	13-07-73
		DE-A- 1668654	15-04-71
		FR-M- 8487	27-07-73
		FR-M- 8494	27-07-73
		FR-A- 1587861	03-04-70
		GB-A- 1211134	04-11-70
		NL-A- 7512107	30-01-76
		NL-A- 6800251	15-07-68
		US-A- 3896157	22-07-75
		US-A- 3904682	09-09-75
		US-A- 4048330	13-09-77
		US-A- 4207241	10-06-80
ZA-A-6707597		NONE	
DE-A-1443429	24-10-68	FR-M- 3124	
		GB-A- 971700	
		US-A- 3228831	
		US-A- 3385886	
		US-A- 3385887	
GB-A-971700		DE-A,B,C 1443429	24-10-68
		FR-M- 3124	
		US-A- 3228831	
		US-A- 3385886	
		US-A- 3385887	
US-A-3758544	11-09-73	US-A- 3873594	25-03-75
		CH-A- 554306	30-09-74
		CH-A- 554826	15-10-74
		CH-A- 535735	15-04-73
		DE-A- 1934460	05-02-70
		GB-A- 1274271	17-05-72
		GB-A- 1274272	17-05-72

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
US-A-3758544		GB-A-	1274273	17-05-72
		NL-A-	6911574	03-02-70
		SE-C-	392263	21-03-77
		US-A-	3637767	25-01-72
DE-A-1934460	05-02-70	CH-A-	554306	30-09-74
		CH-A-	554826	15-10-74
		CH-A-	535735	15-04-73
		GB-A-	1274271	17-05-72
		GB-A-	1274272	17-05-72
		GB-A-	1274273	17-05-72
		NL-A-	6911574	03-02-70
		SE-C-	392263	21-03-77
		US-A-	3637767	25-01-72
		US-A-	3758544	11-09-73
DE-A-2814556	12-10-78	JP-C-	1173362	28-10-83
		JP-A-	53135958	28-11-78
		JP-B-	58004699	27-01-83
		JP-C-	1310718	11-04-86
		JP-A-	53127444	07-11-78
		JP-B-	60034539	09-08-85
		JP-C-	1310723	11-04-86
		JP-A-	54016458	07-02-79
		JP-B-	60034540	09-08-85
		BE-A-	869097	18-01-79
		CA-A-	1113113	24-11-81
		CH-A-	633515	15-12-82
		FR-A,B	2395256	19-01-79
		GB-A-	1580113	26-11-80
		NL-A,B,C	7803644	09-10-78
		SE-B-	437261	18-02-85
		SE-A-	7803848	06-10-78
		US-A-	4161538	17-07-79
WO-A-9412463	09-06-94	AU-B-	5624194	22-06-94
WO-A-9404484	03-03-94	CA-A-	2120942	03-03-94
		EP-A-	0609415	10-08-94

INTERNATIONAL SEARCH REPORT

Int. ional Application No
PCT/EP 94/03182

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07C203/04 C07D487/04 C07D209/28 A61K31/40 A61K31/405
A61K31/21 //(C07D487/04,209:00,209:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07C C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DE,A,17 93 828 (SYNTEX CORP.) 22 April 1976 see the whole document & ZA,A,6 707 597 (...) cited in the application ---	1-18
A	DE,A,14 43 429 (BOOTS PURE DRUG COMPANY LTD.) 24 October 1968 see the whole document & GB,A,971 700 (...) cited in the application ---	1-18
A	US,A,3 758 544 (SYNTEX CORP.) 11 September 1973 see abstract; claims & DE,A,19 34 460 (...) 23 June 1977 cited in the application --- -/--	1-18

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 December 1994	-4. 01. 95

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Paisdor, B

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DE,A,28 14 556 (SANKYO CO., LTD.) 12 October 1978 cited in the application see claims	1-18
P,A	WO,A,94 12463 (HCT-HEALTH CARE TRADING LTD.) 9 June 1994 see abstract; claims	1-18
P,A	WO,A,94 04484 (CORLAY S.L. & METGROVE LTD.) 3 March 1994 see abstract; claims	1-18

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. ional Application No
PCT/EP 94/03182

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE-A-1793828	22-04-76	DE-A,B,C 1793825	05-02-76
		CA-A- 960689	07-01-75
		CA-A- 991655	22-06-76
		CH-A- 517690	15-01-72
		CH-A- 520644	31-03-72
		CH-A- 520645	31-03-72
		CH-A- 537369	13-07-73
		DE-A- 1668654	15-04-71
		FR-M- 8487	27-07-73
		FR-M- 8494	27-07-73
		FR-A- 1587861	03-04-70
		GB-A- 1211134	04-11-70
		NL-A- 7512107	30-01-76
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		US-A- 3904682	09-09-75
		US-A- 4048330	13-09-77
		US-A- 4207241	10-06-80
ZA-A-6707597		NONE	
DE-A-1443429	24-10-68	FR-M- 3124	
		GB-A- 971700	
		US-A- 3228831	
		US-A- 3385886	
		US-A- 3385887	
GB-A-971700		DE-A,B,C 1443429	24-10-68
		FR-M- 3124	
		US-A- 3228831	
		US-A- 3385886	
		US-A- 3385887	
US-A-3758544	11-09-73	US-A- 3873594	25-03-75
		CH-A- 554306	30-09-74
		CH-A- 554826	15-10-74
		CH-A- 535735	15-04-73
		DE-A- 1934460	05-02-70
		GB-A- 1274271	17-05-72
		GB-A- 1274272	17-05-72

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. ional Application No
PCT/EP 94/03182

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
US-A-3758544		GB-A-	1274273	17-05-72
		NL-A-	6911574	03-02-70
		SE-C-	392263	21-03-77
		US-A-	3637767	25-01-72
DE-A-1934460	05-02-70	CH-A-	554306	30-09-74
		CH-A-	554826	15-10-74
		CH-A-	535735	15-04-73
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		GB-A-	1274272	17-05-72
		GB-A-	1274273	17-05-72
		NL-A-	6911574	03-02-70
		SE-C-	392263	21-03-77
		US-A-	3637767	25-01-72
		US-A-	3758544	11-09-73
DE-A-2814556	12-10-78	JP-C-	1173362	28-10-83
		JP-A-	53135958	28-11-78
		JP-B-	58004699	27-01-83
		JP-C-	1310718	11-04-86
		JP-A-	53127444	07-11-78
		JP-B-	60034539	09-08-85
		JP-C-	1310723	11-04-86
		JP-A-	54016458	07-02-79
		JP-B-	60034540	09-08-85
		BE-A-	869097	18-01-79
		CA-A-	1113113	24-11-81
		CH-A-	633515	15-12-82
		FR-A,B	2395256	19-01-79
		GB-A-	1580113	26-11-80
		NL-A,B,C	7803644	09-10-78
		SE-B-	437261	18-02-85
		SE-A-	7803848	06-10-78
		US-A-	4161538	17-07-79
WO-A-9412463	09-06-94	AU-B-	5624194	22-06-94
WO-A-9404484	03-03-94	CA-A-	2120942	03-03-94
		EP-A-	0609415	10-08-94

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
HF 9428+9429		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP 94/ 03182	23/09/1994	06/10/1993
International Patent Classification (IPC) or national classification and IPC		
C07C203/04		
Applicant		
NICOX LIMITED et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   [X] This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consists of a total of 2 sheets.

3. This report contains indications and corresponding pages relating to the following items:

   - I [X] Basis of the report
   - II [ ] Priority
   - III [ ] Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV [ ] Lack of unity of invention
   - V [X] Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI [X] Certain documents cited
   - VII [ ] Certain defects in the international application
   - VIII [ ] Certain observations on the international application

Date of submission of the demand	Date of completion of this report
25/04/1995	16.01.96
Name and mailing address of the IPEA	Authorized officer B. PAISDOR
European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Netherlands Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Telephone No.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
EP94/03182

I. Basis of the report

1. This report has been drawn up on the basis of:

☐ the international application as originally filed

☒ the description, pages 1 - 18, 20 - 31 as originally filed
pages filed with the demand
page 19 , filed with the letter of 10.10.95

☒ the Claims No. 1 - 9, 14 (part), 15 - 18 as originally filed
No. as amended under Article 19
No. , filed with the demand
No. 10 - 14 (part) , filed with the letter of 10.10.95

☐ the drawings, sheets / fig. as originally filed
sheets / fig. , filed with the demand
sheets / fig. , filed with the letter of

2. The amendments have resulted in the cancellation of:

☐ pages:

☐ Claims No.

☐ drawings, sheets / fig.

3. ☐ This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2 c)).

4. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty	Claims	1 - 18	YES
Inventive Step	Claims	1 - 18	YES
Industrial Applicability	Claims	1 - 10, 15 - 18	YES
	Claims	11 - 14	SEE BELOW

2. Citations and Explanations

2.1 The following documents have been considered for the purposes of this report:

D1 WO,A,94/12463
D2 WO,A,94/04484
D3 DE,A,2814556

2.2 Novelty (Article 33(2) PCT)

2.2.1 In document D3 substituted phenylacetic acid derivatives having anti-inflammatory activity is disclosed. The compounds of formula (I) of D3 can be compared with the structurally closely related compounds of the present claim 1, in which the group M of formula (IA) is represented by a group (XXXIII) wherein the substituent R is a group (X). In contrast to D3 the compounds of claim 1 of the present application are either esters or amides containing a nitric ester functional group of these acetic acid derivatives. Therefore claim 1 of this application represents novel subject-matter.

2.2.2 Consequently, the other independent (use) claims 11 - 14, the claims 15 and 16 pertaining to processes for the preparation of compounds of the principal claim, the claims 17 and 18 for pharmaceutical compositions containing the compounds of claim 1 and the remaining dependent claims 2 - 10 are also novel in the sense of Article 33(2) PCT.

2.3 Inventive Step (Article 33(3) PCT)

2.3.1 Document D3, which is considered to represent the most relevant state of the art, discloses (cf., e.g. page 23, table) substituted phenylacetic acid and phenylpropionic acid derivatives having anti-inflammatory and analgetic activity from which the subject-matter of claim 1 differs only in that it pertains to nitric esters of amide and/or ester derivatives of formula (IA). To show this distinguishing structural feature, example 1 of D3 (cf. page 24) can be compared with a compound according to claim 1 in which the groups A and B are hydrogen, n is 1, Y is oxygen and M represents a group (XXXIII) in which R represents a group (X).

2.3.2 The technical problem to be solved by the present invention may therefore be regarded as to provide **further** phenylpropionic and/or phenylacetic acid derivatives having anti-inflammatory and analgesic activity.

2.3.3 Nowhere in the prior art documents being currently on file an indication for a person skilled in the art can be found that nitric ester derivatives of the phenylpropionic acid compounds (for example) known from D3 might also possess the same pharmacological activities. Therefore an inventive step in the sense of Article 33(3) PCT is acknowledged for the compounds of claim 1.

2.3.4. Consequently, the claims 2 - 10 depending on claim 1 and the remaining independent claims 11 - 18 which refer to the preparation, and the application of the novel and inventive compounds according to claim 1 also represent inventive subject-matter.

2.4 For the assessment of the present claims 11 - 14 on the question whether they are industrially applicable, no unified criteria exist in the PCT. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but will allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

VI. **Certain documents cited**

1. Certain published documents (Rule 70.10)

Application no. Patent No.	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date (valid claim) *(day/month/year)*
WO,A,94/12463	09/06/94	15/11/93	26/11/92
WO,A,94/04484	03/03/94	20/06/93	20/08/92

These documents **could** be relevant for the assessment of inventive step of the present application (cf. Rule 64(3) PCT).

WO,A,94/12463 (D1) discloses nitric esters with an anti-inflammatory and/or anti-platelet aggregation activity; the groups Y, A and B of the compounds of general formula (I) (cf. D1, page 3) are the same as in this application. The meaning of the numeral n is identical and the substituent R^2 can be hydrogen or methyl as in the compounds of formula (IA) of the present claim 1. The distinguishing structural feature consists in the group R of D1 as can be shown by comparing, e.g. compound (XVIII) (cf. page 18 of D1) with example 1 of this application (cf. formula (IV), page 19).

In WO,A,94/04484 (D2) nitric esters of 2-(2,6-di-halophenylamino)phenylacetic acid also having, e.g. anti-inflammatory activity are disclosed. Again, the groups Y, A, B and the numeral n of D2 have the same meaning as in the present application. The comparison of e.g. compound (II) (cf. page 9, D2) with a compound according to claim 1 in which the group M represents a group (XXXI) and Y, A, B and n are the same as in formula (IV) (cf. page 19) shows that the distinguishing structural feature consists in the dihalophenylaminophenyl group of D2.

PATENT COOPERATION TREATY

PCT

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:
SAMA, Daniele
SAMA PATENTS
Via Masera, 10
I-20129 Milano
ITALIE

SAMA PATENTS
22 GEN 1996
RECEIVED

NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	16. 01. 96
IMPORTANT NOTIFICATION	
Applicant's or agent's file reference: HF 9428+9429	
International application No.: PCT/EP 94/03182	International filing date *(day/month/year)*: 23/09/1994
Priority date *(day/month/year)*: 06/10/1993	
Applicant: NICOX LIMITED et al.	

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA

European Patent Office, P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk - Netherlands
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
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Authorized officer

E. Reisinger

Telephone No.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
HF 9428+9429		
International application No.	International filing date (*day/month/year*)	Priority date (*day/month/year*)
PCT/EP 94/ 03182	23/09/1994	06/10/1993
International Patent Classification (IPC) or national classification and IPC		
C07C203/04		
Applicant		
NICOX LIMITED et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   [X] This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consists of a total of 2 sheets.

3. This report contains indications and corresponding pages relating to the following items:

   - I [X] Basis of the report
   - II [ ] Priority
   - III [ ] Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV [ ] Lack of unity of invention
   - V [X] Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI [X] Certain documents cited
   - VII [ ] Certain defects in the international application
   - VIII [ ] Certain observations on the international application

Date of submission of the demand	Date of completion of this report
25/04/1995	16.01.96
Name and mailing address of the IPEA	Authorized officer B. PAISDOR
European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Netherlands Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Telephone No.

I. Basis of the report

1. This report has been drawn up on the basis of:

☐ the international application as originally filed

☒	the description. pages	1 - 18, 20 - 31	as originally filed	
	pages		filed with the demand	
	page	19	. filed with the letter of	10.10.95
☒	the Claims No.	1 - 9, 14 (part), 15 - 18	as originally filed	
	No.		as amended under Article 19	
	No.		. filed with the demand	
	No.	10 - 14 (part)	. filed with the letter of	10.10.95
☐	the drawings. sheets / fig.		as originally filed	
	sheets / fig.		. filed with the demand	
	sheets / fig.		. filed with the letter of	

2. The amendments have resulted in the cancellation of:

☐ pages:

☐ Claims No.

☐ drawings. sheets / fig.

3. ☐ This opinion has been established as if (some of) the amendments had not been made. since they have been considered to go beyond the disclosure as filed (Rule 70.2 c)).

4. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty	Claims	1 - 18	YES
Inventive Step	Claims	1 - 18	YES
Industrial Applicability	Claims	1 - 10, 15 - 18	YES
	Claims	11 - 14	SEE BELOW

2. Citations and Explanations

2.1 The following documents have been considered for the purposes of this report:

D1 WO,A,94/12463
D2 WO.A.94/04484
D3 DE,A,2814556

2.2 Novelty (Article 33(2) PCT)

2.2.1 In document D3 substituted phenylacetic acid derivatives having anti-inflammatory activity is disclosed. The compounds of formula (I) of D3 can be compared with the structurally closely related compounds of the present claim 1, in which the group M of formula (IA) is represented by a group (XXXIII) wherein the substituent R is a group (X). In contrast to D3 the compounds of claim 1 of the present application are either esters or amides containing a nitric ester functional group of these acetic acid derivatives. Therefore claim 1 of this application represents novel subject-matter.

2.2.2 Consequently, the other independent (use) claims 11 - 14, the claims 15 and 16 pertaining to processes for the preparation of compounds of the principal claim, the claims 17 and 18 for pharmaceutical compositions containing the compounds of claim 1 and the remaining dependent claims 2 - 10 are also novel in the sense of Article 33(2) PCT.

2.3 Inventive Step (Article 33(3) PCT)

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2.3.2 The technical problem to be solved by the present invention may therefore be regarded as to provide **further** phenylpropionic and/or phenylacetic acid derivatives having anti-inflammatory and analgesic activity.

2.3.3 Nowhere in the prior art documents being currently on file an indication for a person skilled in the art can be found that nitric ester derivatives of the phenylpropionic acid compounds (for example) known from D3 might also possess the same pharmacological activities. Therefore an inventive step in the sense of Article 33(3) PCT is acknowledged for the compounds of claim 1.

2.3.4. Consequently, the claims 2 - 10 depending on claim 1 and the remaining independent claims 11 - 18 which refer to the preparation, and the application of the novel and inventive compounds according to claim 1 also represent inventive subject-matter.

2.4 For the assessment of the present claims 11 - 14 on the question whether they are industrially applicable, no unified criteria exist in the PCT. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but will allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

Application no. Patent No.	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (valid claim) (day/month/year)
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WO,A,94/04484	03/03/94	20/06/93	20/08/92

These documents **could** be relevant for the assessment of inventive step of the present application (cf. Rule 64(3) PCT).

WO,A,94/12463 (D1) discloses nitric esters with an anti-inflammatory and/or anti-platelet aggregation activity; the groups Y, A and B of the compounds of general formula (I) (cf. D1, page 3) are the same as in this application. The meaning of the numeral n is identical and the substituent R^2 can be hydrogen or methyl as in the compounds of formula (IA) of the present claim 1. The distinguishing structural feature consists in the group R of D1 as can be shown by comparing, e.g. compound (XVIII) (cf. page 18 of D1) with example 1 of this application (cf. formula (IV), page 19).

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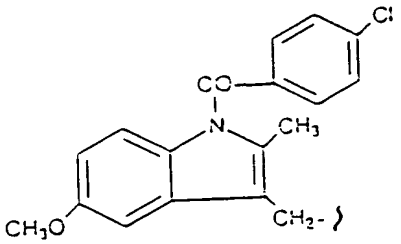
n is equal to four.

10. Derivatives of 1-(p- chlorobenzoyl) -5-methoxy - 2-methyl-3-indolylacetic acid according to claim 1, characterized in that M is equal to



(XXXII)

A and B are equal to hydrogen, Y is equal to oxygen and n is equal to four.

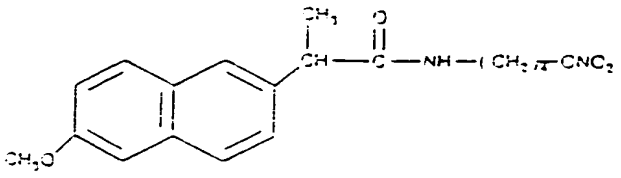
11. The use of Nitric esters according to claim 1 characterized in that they are utilizable in the pharmaceutical field as anti-inflammatory agents.

12. The use of Nitric esters according to claim 1 characterized in that they are utilizable in the pharmaceutical field as analgesic agents.

13. The use of Nitric esters according to claim 1 characterized in that they are utilizable in the treatment of rheumatic illnesses, in the treatment of disorders of an immunologic nature and of the moderate to medium painful states.

14. The use of Nitric esters according to claim 1 characterized in that they are utilizable in the treatment of the diseases of the cardiovascular system, in the treatment

Always according to the processes subject matter of the present invention, also the preparation of a nitric ester derivated from propionic acid proved to be particularly advantageous, having the following formula:



(IV)

which is prepared as described in the following example, that is given hereunder as a mere indication and which does not limit in any way the protection scope of this invention.

EXAMPLE 2

a) 23.9 g of potassium-phtalimide dispersed into 200 ml of anhydrous dimethylformamide were added to a solution of 55.7 g of 1,4-di bromo-butane dissolved in 300 ml of anhydrous dimethylformamide.

The reaction mixture was agitated for 12 hours at room temperature, then diluted with water and extracted with methylene chloride. The methylene chloride was evaporated from the organic phase so obtained at a reduced pressure and then the dimethylformamide was removed by distillation at the pressure of 1.33 KPa (10 mm Hg.)

The residue was regained with water and extracted with methylene chloride.

INTERNATIONAL SEARCH REPORT

Int. Application No
PCT/EP 94/03182

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07C203/04 C07D487/04 C07D209/28 A61K31/40 A61K31/405
A61K31/21 //(C07D487/04,209:00,209:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07C C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DE,A,17 93 828 (SYNTEX CORP.) 22 April 1976 see the whole document & ZA,A,6 707 597 (...) cited in the application	1-18
A	DE,A,14 43 429 (BOOTS PURE DRUG COMPANY LTD.) 24 October 1968 see the whole document & GB,A,971 700 (...) cited in the application	1-18
A	US,A,3 758 544 (SYNTEX CORP.) 11 September 1973 see abstract; claims & DE,A,19 34 460 (...) 23 June 1977 cited in the application	1-18

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 December 1994	-4. 01. 95

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Paisdor, B

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DE,A,28 14 556 (SANKYO CO., LTD.) 12 October 1978 cited in the application see claims	1-18
P,A	WO,A,94 12463 (HCT-HEALTH CARE TRADING LTD.) 9 June 1994 see abstract; claims	1-18
P,A	WO,A,94 04484 (CORLAY S.L. & METGROVE LTD.) 3 March 1994 see abstract; claims	1-18

INTERNATIONAL SEARCH REPORT

Information on patent family members

[redacted] ional Application No
PCT/EP 94/03182

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		CH-A- 520644	31-03-72
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		GB-A- 1274272	17-05-72

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		GB-A-	1274272	17-05-72
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		EP-A-	0609415	10-08-94

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C07C 203/04, C07D 487/04, 209/28, A61K 31/40, 31/405, 31/21 // (C07D 487/04, 209:00, 209:00)

A1

(11) International Publication Number: WO 95/09831

(43) International Publication Date: 13 April 1995 (13.04.95)

(21) International Application Number: PCT/EP94/03182

(22) International Filing Date: 23 September 1994 (23.09.94)

(30) Priority Data:
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MI94/A000916 10 May 1994 (10.05.94) IT

(71) Applicant *(for all designated States except US)*: NICOX LIMITED [IE/IE]; 17 Dame Street, Dublin 2 (IE).

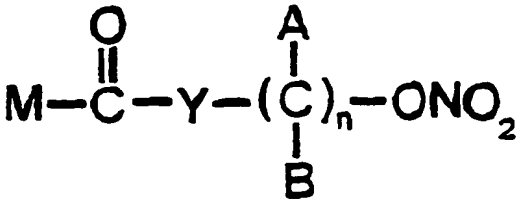
(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: DEL SOLDATO, Piero [IT/IT]; Via E. Toti, 22, I-20052 Monza (IT).

(74) Agent: TRUPIANO, Roberto; Brevetti Europa S.r.l., Piazza Bernini, 6, I-20133 Milano MI (IT).

(81) Designated States: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, JP, KG, KP, KR, KZ, LK, LR, LT, LV, MD, MG, MN, NO, NZ, PL, RO, RU, SI, SK, TJ, TT, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ).

Published
With international search report.

(54) Title: NITRIC ESTERS HAVING ANTI-INFLAMMATORY AND/OR ANALGESIC ACTIVITY AND PROCESS FOR THEIR PREPARATION



(IA)

(57) Abstract

The present invention refers to nitric esters of derivatives of propionic acid, 1-(p-chlorobenzoyl)-5-methoxy-2-methyl-3-indolylacetic acid, 5-benzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid, 6-methoxy-2-naphthylacetic acid, having general formula (IA), their pharmaceutical use and the process for their preparation.

NITRIC ESTERS HAVING ANTI-INFLAMMATORY AND/OR ANALGESIC ACTIVITY AND PROCESS FOR THEIR PREPARATION.

OBJECT OF THE INVENTION

The present invention refers to nitric esters of derivatives of propionic acid, 1-(p-chlorobenzoyl)-5-methoxy-2-methyl -3-indolylacetic acid, 5-benzoyl -1,2-dihidro -3H- pyrrolo[1,2-a]pyrrole -1-carboxylic acid, 6-methoxy -2-naphthylacetic acid, their pharmaceutical utilization and the process for their preparation. The present invention also refers to pharmaceutical compositions comprising at least one of said nitric esters as active constituent.

PRIOR ART

Some derivatives of propionic acid, such as, for instance, 2-(6-methoxy-2-naphtyl)propionic acid 2-(4-isobutylphenyl)propionic acid or alpha-Methyl-4-[(2-oxocyclopentyl)methyl]benzeneacetic acid, have been used for a long time in the pharmaceutical field for their anti-inflammatory activity and have been present for many years on the different world markets. The process for the preparation of 2-(6-methoxy-2-naphtyl)propionic acid has been described in the South African Patent N°6707,597, in the German Patent N° 1,934,460, corresponding to the US Patent N°3,637,767 and also in C.A.71,91162j (1969); HARRISON et al. J.Med.Chem. 13,203 (1970); the process for the preparation of 2-(4-isobutylphenyl)propionic acid has been

described in Patents GB N°971,700, US N°3,228,831 and US N°3,385,886, and also in T. SHIORI, N. KAWAI, J.Org. Chem. 43,2936 (1978); J.T. PINHEY, B.A. ROWE, Tetrahedron Letters 21, 965 (1980);while the process for the preparation of alpha-methyl-4-[(2-oxocyclopentyl)methyl]benzenacetic acid has been described in the German Patent N°2,814,556 and in US Patent N°4,161,538.

In the case of 2-(6-methoxy-2-naphtyl)propionic acid, the pharmacological profile is described in ROSZKOWSKI et al. J. Pharmacol. Exp. Ther. 179,114 (1971), while the pharmacological profile of 2-(4-isobutylphenyl)propionic acid is reported in ADAMS et al. Arch. Pharmacodyn. Ther. 178,115 (1969).

The utilization of these derivatives of propionic acid as anti-inflammatory agents involves, as known, extremely severe adverse reactions affecting, for instance, the gastrointestinal system, as well as damages to liver and kidneys.

Other particularly toxic products are, for example, 5-benzoyl -,2- dihydro-3H- pyrrolo[1,2-a] pyrrole 1-carboxylic acid or Ketorolac [W.H.ROOKS et al. Agents Actions 12,684 (1982)] and 1-(4-chlorobenzoyl)-5-methoxy-2- methyl- 1H-indole- 3-acetic acid or Indomethacin [C.D.KLAASSEN, Toxicol. Appl.Pharmacol. 28,127 (1976)]. In particular, in some countries Ketorolac has been withdrawn from the market because of its gastrointestinal toxicity, while Indomethacin is one of the

drugs which has caused the highest death-rate from the year of its introduction in the market. Compared with other known anti-inflammatory and/or analgesic drugs, Ketorolac and Indomethacin cause - because of the already described adverse reactions - very extensive damages and, in particular as concerns gastrointestinal toxicity, deaths have been ascertained even in children.

It is therefore evident that there is the need of having drugs which, though providing a good anti-inflammatory and/or analgesic activity, do not result to be, in general, toxic.

OBJECTS OF THE INVENTION

Object of the present invention is that of providing a product which, while assuring at least the maintenance of the pharmacological activity which is characteristic of the known anti-inflammatory and/or analgesic agents, is capable of eliminating the adverse reactions brought about by the treatment with said agents, and has good tolerance.

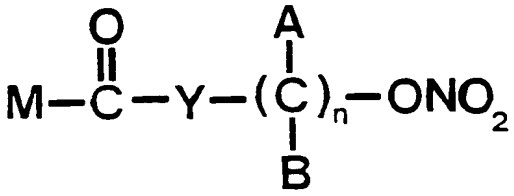
Another object of the present invention is that of realizing a process for the preparation of derivatives of propionic acid, 1-(p-chlorobenzoyl)-5- methoxy-2-methyl -3-indolylacetic acid, 5-benzoyl -1,2-dihidro -3H- pyrrolo[1,2-a]pyrrole -1-carboxylic acid, 6-methoxy -2-naphthylacetic acid, having an anti-inflammatory and/or analgesic activity, good tolerance and being

exempt from the adverse reactions that are typical of anti-inflammatory and analgesic agents.

Still another object of the present invention is that of providing pharmaceutical compositions having anti-inflammatory and/or analgesic activity which results provided with good tolerance.

DESCRIPTION OF THE INVENTION

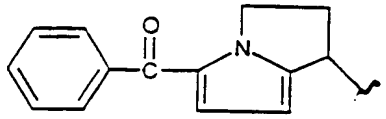
These and still further objects and associated advantages which shall clearly result from the following description, are reached by derivatives of propionic acid, 1-(p-chlorobenzoyl)-5- methoxy-2-methyl -3-indolylacetic acid, 5-benzoyl -1,2-dihidro -3H-pyrrolo[1,2-a]pyrrole -1-carboxylic acid, 6-methoxy -2-naphthylacetic acid which, according to the present invention, have the following general formula:



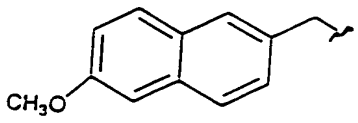
(IA)

where:

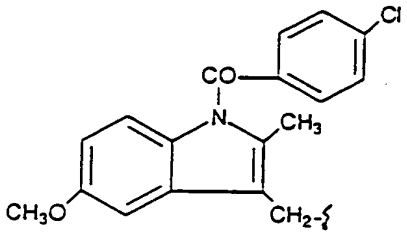
A and B are chosen among hydrogen, linear or branched, substituted or non substituted alkyl chains, M is chosen among:



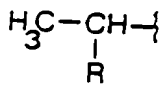
(XXX)



(XXXI)

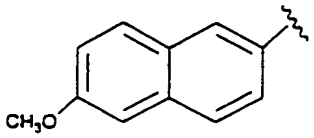


(XXXII)

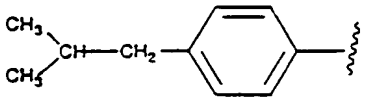


(XXXIII)

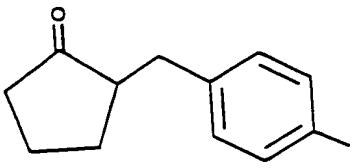
where R is chosen among:



(II)



(III)

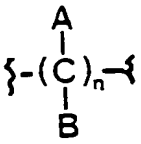


(X)

Y is chosen among oxygen, NH, NR_1, where R_1 is a linear

or branched alkyl group, and n is comprised between 1 and 10.

More particularly, the fragment



is a linear, branched or cyclic alkylenic group C_2-C_{10}.

In fact, it has been observed that the introduction of a group such as a terminal nitric ester in the derivatives (IA) permits to mantain the pharmacological activity which is characteristic of anti-inflammatory non steroidal and/or analgesic agents, leads to products provided with good tolerance, while eliminating the adverse reactions caused by the treatment with such drugs. Furthermore, the introduction of a terminal nitric ester in the derivatives of propionic acid, permits to potentiate the anti-inflammatory effect compared with the well known non-steroidal anti-inflammatory drugs; such increase is made by the terminal nitric ester group, which can be considered as a source of nitric oxide and which can exert additional anti-inflammatory effects.

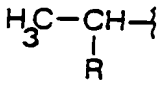
It has been also observed that the derivatives (IA) are useful in the treatment of different unhealthy conditions, for instance unhealthy conditions which required the treatment with both anti-inflammatory and analgesic drug, or rheumatic diseases in general, disorders of an

immunologic nature, and they can also alleviate moderate-medium painful states of any kind.

Moreover, the derivatives (IA) subject matter of this invention, are useful in the treatment of the illnesses of the cardiovascular system and of the central nervous system, in particular in the treatment of myocardial and brain ischemiae, as well as in some cases of arterial thrombosis and in some cases of senile dementia.

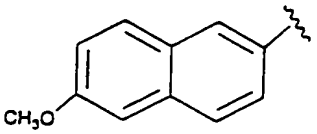
Always according to this invention, a nitric ester (IA) proved to be particularly advantageous, where:

hydrogen is chosen as A and B, M is chosen as



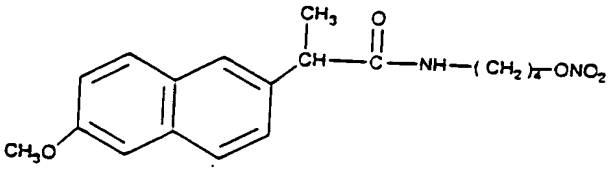
(XXXIII)

where R is chosen as:



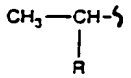
(II)

NH is chosen as Y, and n is equal to four, according to the following formula:



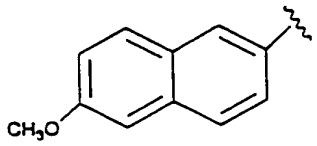
(IV)

A nitric ester (IA) has also proved to be particularly advantageous according to this invention, where: hydrogen is chosen as A and B, M is chosen as



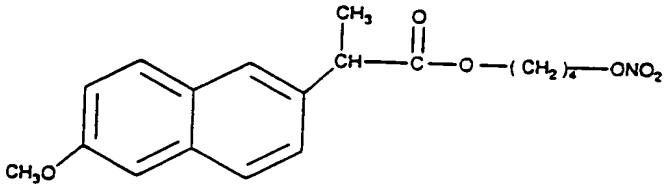
(XXXIII)

where R is chosen as:



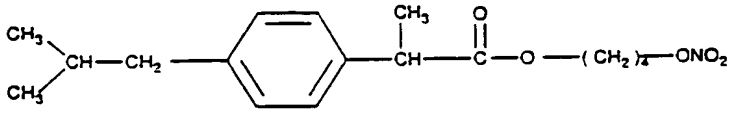
(II)

oxygen is chosen as Y, an n is equal to four, according to the following formula:



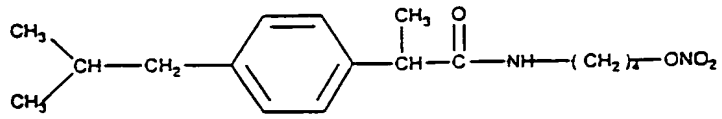
(V)

Also the nitric esters of derivatives of 2-(4-isobutylphenyl)propionic acid have proved to be particularly advantageous according to this invention, having the following formulae:



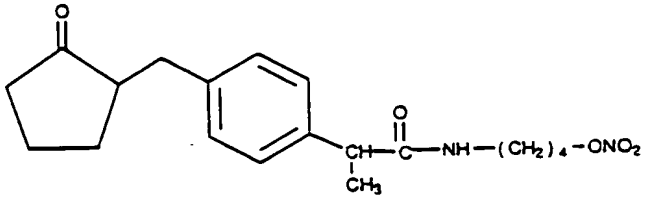
(XIII)

and

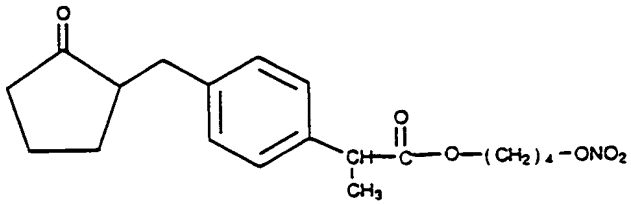


(XIV)

Always according to the present invention, nitric esters (IA) have proved to be particularly advantageous, having the following formulae:

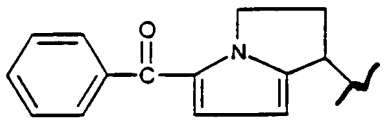


(XI)



(XII)

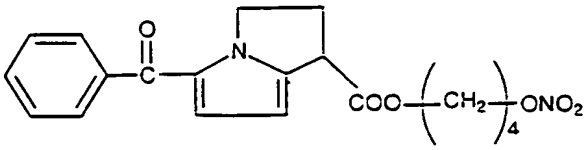
Always according to the present invention, nitric esters (IA) where M is chosen as



(XXX)

oxygen is chosen as Y, hydrogen is chosen as A and B and n is equal to four according to the following

formula:

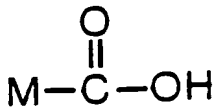


(XXXIV)

proved to have very good tolerance.

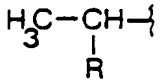
For the preparation of nitric esters (IA) subject matter of the present invention, a first process has proved to be particularly advantageous which, according to the present invention, includes the following steps:

- Preparation of sodium salt of derivatives having the following general formula:



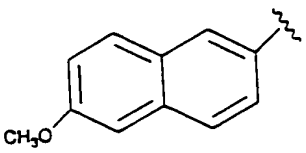
(VIA)

where M is chosen among (XXX), (XXXI), (XXXII),

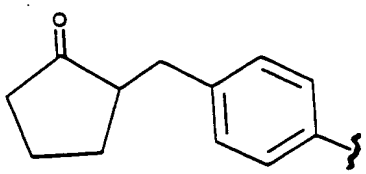


(XXXIII)

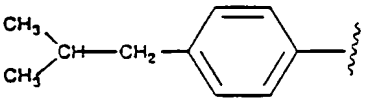
where R is chosen among the following structures:



(II)



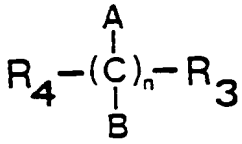
(X)



(III)

or preparation of derivatives (VIA) functionalized to the carboxylic group as acylic chlorides, anhydrides or the like;

- Reaction between the sodium salt of said derivatives (VIA) or of said derivatives (VIA) functionalized to the carboxylic group, with a composition having the following general formula:



(VII)

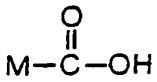
where:

R_4 is chosen among chlorine, bromine, NHR_5 with R_5 hydrogen, linear or branched alkyl chain, A and B are chosen among hydrogen, linear or branched, substituted or non substitutes alkyl chains, R_3 is chosen among chlorine, bromine and iodine, and n is comprised between 1 and 10, with ensuing production of the relevant monomeric esters or the relevant amides;

- Reaction of said monomeric esters or said amides with a nitrating agent such as $AgNO_3$ or the like, with ensuing production of nitric esters (IA).

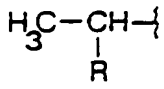
A second process has also proved to be particularly advantageous which, always according to the present invention, includes the following steps:

- Preparation of sodium salt of derivatives having the following general formula:



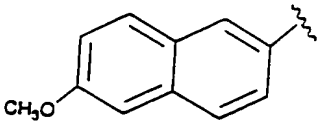
(VIA)

where M is chosen among (XXX), (XXXI), (XXXII),

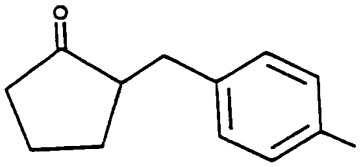


(XXXIII)

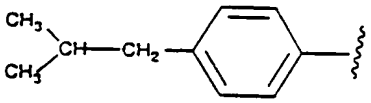
where R is chosen among the following structures:



(II)



(X)

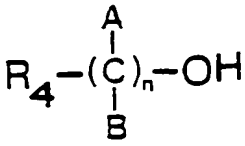


(III)

or preparation of derivatives (VIA) functionalized to the carboxylic group, such as acylic chlorides, anhydrides or the like;

- Reaction between the sodium salt of said derivatives (VIA) or of said derivatives (VIA) functionalized to the carboxylic group, with a composition having the

following general formula:



(VIII)

where;

R_4 is chosen among chlorine, bromine, NHR_5 with R_5 hydrogen, linear or branched alkyl chains, A and B are chosen among hydrogen, linear or branched, substituted or non substituted alkyl chains, and n is comprised between 1 and 10, with ensuing production of the relevant monomeric esters or the relevant amides;

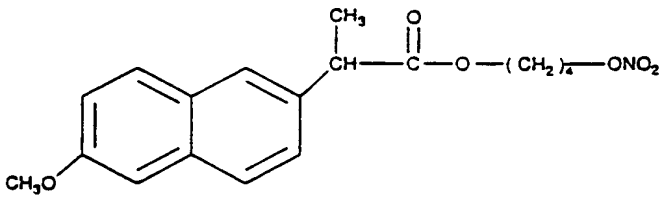
- Reaction of said monomeric esters or said amides with an halogenating composition such as PBr_3 or the like, with ensuing prouction of said monomeric esters or said amides characterized by the presence of a terminal halogen group;

- Reaction of said monomeric esters or said amides characterized by the presence of a terminal halogen group, with a nitrating agent such as $AgNO_3$ or the like, with ensuing production of nitric esters of derivatives (IA).

The solvents which are utilized in the processes subject matter of the present invention are preferably chosen among chloroform, methylene chloride, acetonitrile, dimethylformamide, tetrahydrofuran, 1,4-dioxane and the like.

Such processes for the preparation of derivatives (IA), subject matter of the present invention, consist of a limited number of steps, which permits to obtain in a short time the products which derive from these processes, with satisfactory yields and in high amounts, also on the industrial level.

According to the processes subject matter of this invention, the preparation of a nitric ester derived from propionic acid has proved to be particularly advantageous, having the following formula:



(V)

which is prepared as described in the example that is given hereunder as a mere indication and which does not limit in any way the protection scope of the invention.

EXAMPLE 1

a) 0.59 g of EtONa dissolved in 10 ml of ethyl alcohol were added, by slow dripping, to a solution of 2 g of 2-(6-methoxy-2-naphtyl)propionic acid, dissolved in 20 ml of ethyl alcohol. The reaction mixture was stirred for 5 minutes at room temperature, then the solvent was evaporated at a reduced pressure, obtaining 2.1 g of sodium salt of 2-(6-methoxy-2-naphtyl)propionic acid.

The 2.1 g of sodium salt of 2-(6-methoxy-2-naphtyl)

propionic acid so obtained were disperded in 40 ml of dimethylformamide and 1.5 g of 1-Br-4-Cl-butane dissolved in 30 ml of dimethylformamide were added by dripping to this dispersion. The reaction mixture was stirred for 12 hours at room temperature, then diluted with water and extracted with methylene chloride. The organic phase so extracted was anhydrified on sodium sulfate and the solvent was evaporated at a reduced pressure until a dry residue of 2 g was obtained.

The residue was purified by chromatography on silica gel, utilizing an eluting mixture constituted by hexane/ether 7/3 (v/v).

The head fractions were collected, the solvent was evaporated at a reduced pressure and 1 g of 2-(6-methoxy-2-naphtyl)propionate of 4-chlorobutyl (IX) was obtained.

IR(cm^{-1}):C=0,1669.

^{1}H-NMR(300MHz) ($CDCl_3$): 1.6ppm (d,3H); 1.75ppm (m, 4H); 3.45ppm (m, 2H); 3.88ppm (q,1H); 3.91ppm (1,3H); 4.1ppm (m, 2H); 7.1-7-7.7ppm (m, aromatics).

Mass spectrometry (i.e.): $M^{+\cdot}$ 320.

b) 0.79 g of $AgNO_3$ dissolved in 1.3 ml of acetonitrile were dripped to 1 g of (IX) obtained as described in a), dissolved in 4,5 ml of acetonitrile. The reaction mixture was stirred for 12 hours at a temperature of 85°C and then filtered.

From the resulting solution, the solvent was evaporated

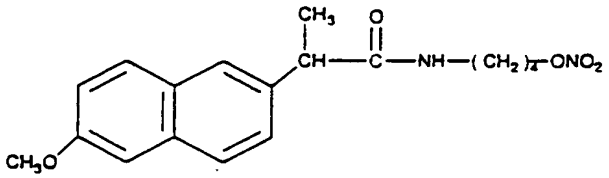
at a reduced pressure, and a residue was obtained to which 10 ml of methylene chloride were added. The mix so obtained was filtered once again, the organic phase was washed with water and then anhydrified on sodium sulfate. The solvent was evaporated under reduced pressure and 1.8 g of a dry residue was obtained, which was purified by chromatography on silica gel, utilizing an eluting mixture constituted by hexane/ether 7/3 (v/v). The fractions containing the product were collected, the solvent was evaporated at a reduced pressure and 1.5 g of nitric ester of 2-(6-methoxy-2-naphtyl)propionate of 4-hydroxy-butyl (V) were obtained.

IR(cm^{-1}): C=0,1733; ONO_2, 1637.

^{1}H-NMR(300MHz) ($CDCL_3$): 1.6ppm (d,3H); 1.65ppm (m, 4H); 3.8ppm (q, 1H); 3.9ppm (s,3H); 4.1ppm (m, 2H); 4.3ppm (m, 2H); 7.1-7.7ppm (m, aromatics).

Mass spectometry (i.e.) $M^{+\cdot}$ 347.

Always according to the processes subject matter of the present invention, also the preparation of a nitric ester derivated from propionic acid proved to be particularly advantageous, having the following formula:



(IV)

which is prepared as described in the following example, that is given hereunder as a mere indication and

which does not limit in any way the protection scope of this invention.

EXAMPLE 2

a) 23.9 g of potassium-phtalimide dispersed into 200 ml of anhydrous dimethylformamide were added to a solution of 55.7 g of 1,4-di bromo-butane dissolved in 300 ml of anhydrous dimethylformamide.

The reaction mixture was agitated for 12 hours at room temperature, then diluted with water and extracted with methylene chloride. The methylene chloride was evaporated from the organic phase so obtained at a reduced pressure and then the dimethylformamide was removed by distillation at the pressure of 10 mm Hg.

The residue was regained with water and extracted with methylene chloride.

Tha organic phase so obtained was anhydrified and the solvent was evaporated at a reduced pressure until 14.8 g of 1-phtalimide-4-bromo-butane were obtained, which were treated with isopropyl ether and then essiccated.

m.p. = 77°C

b) 32 ml of hydriodic acid were cautiously added to 8.25 g of 1-phtalimido-4-bromo-butane; the mixture was then submitted to heating and kept in ebullition for 24 hours.

After cooling, the mixture was diluted with water and after filtration the solvent was evaporated at a reduced pressure, obtaining a residue which, once crystal-

lized by ethyl ether, produced 6 g of 4-iodine-butylammonium iodide.

m.p. = 103°C

c) 7 ml of thionyl chloride were cautiously added to a solution of 2.3 g of 2-(6-methoxy-2-naphtyl)propionic acid in 15 ml of anhydrous chloroform. The reaction mixture was stirred for 40 minutes at room temperature and then the solvent was evaporated at a reduced pressure, obtaining 2.23 g of 2-(6-methoxy-2-naphtyl)propionylchloride.

2.3 g od 2-(6-methoxy-2-naphtyl)propionylchloride were dissolved in pyridine and the solution was cooled at the temperature of 0°C.

3.27 g of 4-iodobutylammonium iodide were added to this solution and the mixture so obtained was agitated for 1 hour at 0°C and then diluted with water and extracted with methylene chloride.

The organic phase so obtained was washed initially with a 10% solution of hydrochloric acid and afterward with a saturated solution of sodium bicarbonate, then the solvent was evaporated at a reduced pressure, obtaining 3.2 g of a dry residue. The residue was purified by chromatography on silica gel, utilizing methylene chloride as eluent.

The intermediate fractions were collected, the solvent was evaporated at a reduced pressure and 1.6 g of 2-(6-methoxy-2-naphtyl)-4-iodobutyl propionamide (XX) were

obtained.

IR (cm^{-1}): NH, 3294; C=0,1651.

^{1}H-NMR(300MHz) ($CDCl_3$): 1.1-1.75 ppm (m, 4H); 1.6ppm (d, 3H); 3.1ppm (t, 2H); 3.2ppm (q, 2H); 3.7ppm (q, 1H); 3.9ppm (s, 3H); 5.35ppm (m, NH); 7.1-7.75ppm (m, aromatics).

d) A suspension of 1.6 g of 2-(6-methoxy-2-naphtyl)-4-iodobutyl propionamide in 20 ml of acetonitrile was heated at a temperature of about 40°C and stirred until a solution was obtained to which 1.0 g of $AgNO_3$ were added.

The mixture was stirred for 1 hour at room temperature, then filtered and the solvent was evaporated at a reduced pressure. The residue obtained was regained with methylene choride, the resulting mixture was filtered and the solvent was evaporated at a reduced pressure, and 0,8 g of dry residue were obtained which were purified by chromatography on silica gel, utilizing an eluting mixture constituted by methylene chloride/ethyl acetate 9/1 (v/v).

The head fractions were collected, the solvent was evaporated at a reduced pressure and 0.75 g of nitric ester of 2-(6-methoxy-2-naphtyl)-4-hydroxybutyl propionamide (IV) were obtained.

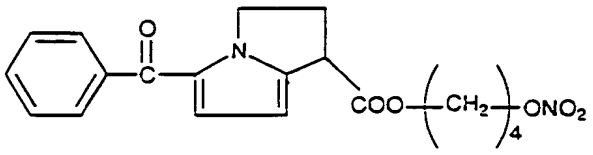
IR(cm^{-1}): C=0,1672; NH, 3294; ONO_2, 1637

Mass spectometry (i.e.) $M^+ \cdot 346$.

^{1}H-NMR(80mhz) ($CDCl_3$): 1.3ppm-1.6ppm (m, 4H);

1.7ppm (d, 3H); 3.1ppm (q, 2H); 3.7ppm (q, 1H); 3.9ppm (s, 3H); 4.3ppm (m, 2H); 5.6ppm (m, NH); 7.05-7.8ppm (m, aromatics).

Always according to the present invention, also the nitric ester having the following formula:

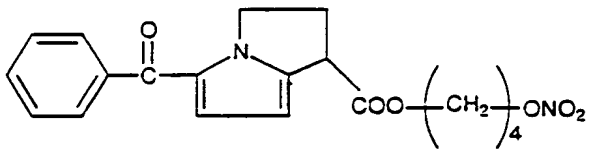


(XXXIV)

proved to be particularly advantageous, which is prepared as described in the following example that is also given hereunder as a mere indication and which does not limit in any way the protection scope of this invention.

EXAMPLE 3

Preparation of the composition having the formula:



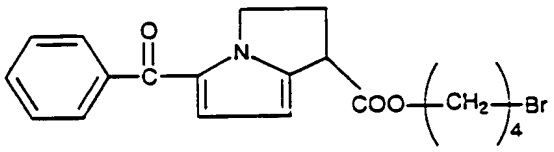
(XXXIV)

a) In a suspension of 80% sodium hydride (0,16 g) in DMF (15 ml), 1,15 g of Ketorolac dissolved in 20 ml of DMF were caused to drip under agitation.

The reaction mix was kept under agitation at 40°C for

15 minutes, then 1 ml of 1,4-dibromobutane was added and the mix was kept under agitation at room temperature overnight.

Then the solvent was evaporated under reduced pressure and the residue was treated with water and methylene chloride. The organic phase was separated, dryed on sodium sulfate and the solvent was removed under reduced pressure, to obtain a residue which was purified by silica gel chromatography, utilizing a 4/6 petroleum ether/ether eluent mix (v/v). The head fractions were collected, the solvent was evaporated under reduced pressure and 0.75 g of product was obtained having the formula:



(XXXV)

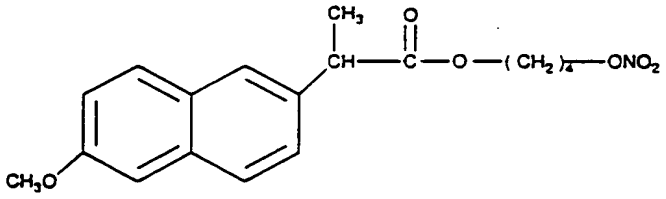
^{1}H-NMR (80 MHz) ($CDCl_3$) (ppm): 1,83(6H, m); 2,81(2H, m); 3,38(2H, t); 4,12(2H, t); 4,48(1H,m); 6,03(1H, d); 6,78(1H,d); 7,41(3H, m); 7,73(2H, m).

b) A solution of $AgNO_3$ (0,5 g) in 5 ml of acetonitrile was added to a solution of (XXXV) (0,75 g) in 20 ml of acetonitrile. The reaction mix was kept stirring at room temperature for 48 hours. The solvent was then removed under pressure and the residue was treated with water and methylene chloride. The organic phase

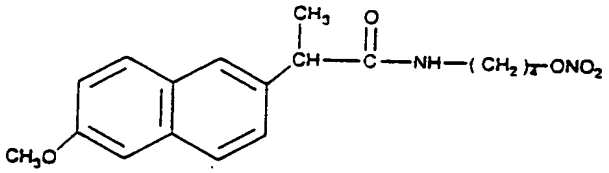
was then separated, dryed on sodium sulfate and the solvent was removed under reduced pressure. The residue was purified by filtration on silica gel, utilizing a 4/6 petroleum ether/ether eluent mix. The head fractions were collected, the solvent was evaporated under reduced pressure and 0.35 g of (XXXIV) were obtained.

^{1}H-NMR (80 MHz) ($CDCl_3$)(ppm): 1.78(6H, m); 2.82(2H, m); 4.14(2H, m); 4.47(3H, m); 6.03(1H, d); 6.79(1H, d); 7.46(3H, m); 7.77(2H, m).

Through biological assays the anti-inflammatory and analgesic activity were determined, for instance of nitric esters (IA) having the following formulae:



(V)



(IV)

The anti-inflammatory activity of said nitric esters of derivatives of propionic acid was determined in Wistar rats utilizing the method of carrageenan edema, as reported in C.A. WINTER, E. RISLEY, G.W. NUSS, Proc. Soc. Exp. Biol. Med. 111,544-547 (1962), while the

analgesic activity of said derivatives was determined in Swiss mice as reported by L.C. HENDERSHOT, J. FORSAITH, J.Pharmacol. Exp. Ter. 125,237-249 (1959).

The anti-inflammatory and analgesic activity of said derivatives resulted to be comparable to 2-(6-methoxy-2-naphtyl)propionic acid taken as a reference.

The anti-platelet aggregation activity of said derivatives was determined on human platelets. Platelets were incubated with the compounds for 10 min at 37°C prior to stimulation with trombin. The anti-platelet aggregation activity of said derivatives resulted to be comparable to 2-(6-methoxy-2 -naphthyl)propionic acid taken as a reference.

Then, the acute toxicity of said derivatives (IV) and (V) was evaluated by oral administration of a single dose of each composition (IV) and (V), utilizing groups of 10 Swiss mice for each derivative.

The incidence of lethality and the onset of a toxic symptomatology were reported for an observation period of 14 days.

Even after the administration of a dose of 750 mg/kg of composition (IV) or composition (V) no apparent toxicity simptoms were observed in the treated animals.

Further biological assays were carried out in order to define the pharmaco-toxicological profile of the studied compounds, in particular of composition (V),

compared with 2-(6-methoxy-2-naphtyl)propionic acid taken as reference.

A. PHARMACODYNAMIC ACTIVITY

ACUTE MODELS

Rat carrageenan paw edema. On the basis of preliminary experiments, the compound (V) and 2-(6-methoxy-2-naphtyl)propionic acid prove to have a comparable efficacy; the effective dose is comprised in the range from 1 to 10 mg/kg p.o.

SUBACUTE MODELS

Rat adjuvant arthritis. The animals treated for 19 running days (from the 3rd to the 20th day after the inducing injection) with composition (V) or with 2-(6-methoxy-2-naphtyl)propionic acid, both of them at doses of 3 mg/kg p.o., showed a significant and comparable reduction in arthritic symptomatology compared with controls.

B. GASTROINTESTINAL TOLERABILITY

Damage to the gastric mucosa of the rat. The compound (V) was studied in comparison with 2-(6-methoxy-2-naphtyl)propionic acid taken as reference, both of them at doses comprised between 3 and 30 mg/kg p.o.; the compound (V) proved to be significantly better tolerated than 2-(6-methoxy-2-naphtyl)propionic acid. 2-(6-methoxy-2-naphtyl)propionic acid already at 3 mg/kg caused gastric damages, and such effects resulted to be dose-dependent, while the compound (V) proved to be

well tolerated even at doses of 30 mg/kg.

C. GENERAL PHARMACOLOGY

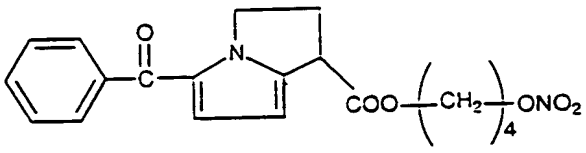
A secondary pharmacological evaluation of compound (V) was carried out in comparison with 2-(6-methoxy-2-naphtyl)propionic acid. No considerable additional effects with respect to the primary pharmacological activity were observed on central nervous system, on the autonomous system, on the cardiovascular, respiratory and gastrointestinal systems.

D. TOXICOLOGY

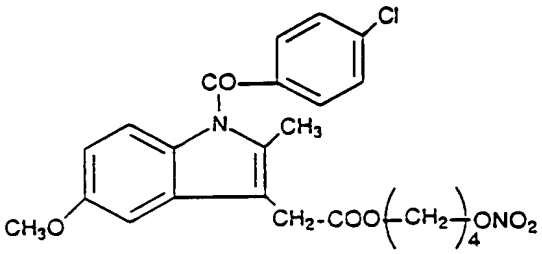
Acute toxicity in rodents. Preliminary studies were carried out in rodents, utilizing two administration routes. No simptoms of apparent toxicity were observed in animals treated with oral or intraperitoneal doses of 300 mg/kg.

Maximum tolerated dose in non-rodents. Preliminary studies have indicated that compound (V) was very well tolerated in the dog, an animal species which is known to be particularly sensitive to the ulcerogenic activity of anti-inflammatory agents in general. The animals received increasing oral doses of compound (V) up to 30 mg/kg and no apparent symptoms were observed. In comparison, 2-(6-methoxy-2-naphtyl)propionic acid, administered at doses of 10 mg/kg, caused the death of the animals.

Furthermore, biological studies concerning nitric esters (IA) having the following formulae:



(XXXIV)



(XXXVI)

were carried out.

Then the anti-inflammatory activity, the gastrointestinal tolerability and the platelet anti-aggregating activity of the above compositions were determined.

The anti-inflammatory activity was determined by the method of the carrageenan edema in the rat, as described by C.A.WINTER et al. (1962) Proc.Soc.Exp.Biol.Med. 111,544. The gastrointestinal tolerability was evaluated by oral administration in the rat. The platelet anti-aggregating activity was determined on human platelets stimulated by arachidonic acid, according to the method described by V.BERTELE et al. (1983) Science 220, 517.

The results are shown on Table 1 as values concerning the anti-inflammatory, anti-aggregating activity and the gastrointestinal tolerability of the compositions

under examination, expressed as a power ratio relatively to the basic product taken as a unity standard.

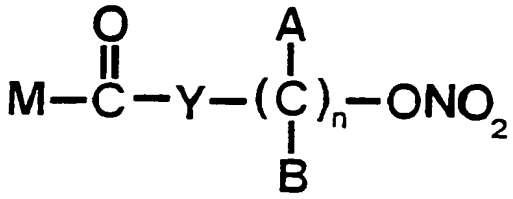
TABLE 1

COMPOSITION	ANTI-INFLAMM. ACTIVITY	ANTI-AGGREG. ACTIVITY	GASTROINTEST. ULCEROGEN.
(XXXIV)	1,25	1,10	0,15
KETOROLAC	1,0	1,0	1,0
(XXXVI)	1,0	1,30	0,1
INDOMETHACIN	1,0	1,0	1,0

The acute toxicity of the compositions under examination has been approximately evaluated by oral administration of a single dosage of the substance to groups of 10 mice. The death-rate incidence and the onset of toxic symptoms have been observed for a period of 14 days. Even after the administration of 100 mg/kg of each composition, the animals did not show any symptom of apparent toxicity.

CLAIMS

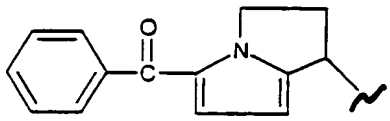
1. Derivatives of propionic acid, 1-(p-chlorobenzoyl) -5- methoxy-2-methyl -3-indolylacetic acid, 5-benzoyl -1,2-dihidro -3H- pyrrolo[1,2-a]pyrrole -1-carboxylic acid, 6-methoxy -2-naphthylacetic acid, characterized in that they have the following general formula:



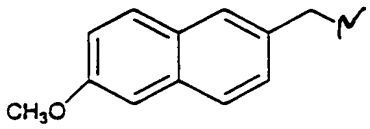
(IA)

where:

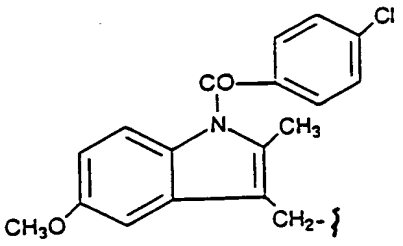
A and B are chosen among hydrogen, linear or branched, substituted or non substituted alkyl chains, M is chosen among:



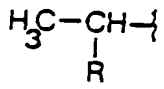
(XXX)



(XXXI)

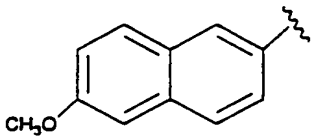


(XXXII)

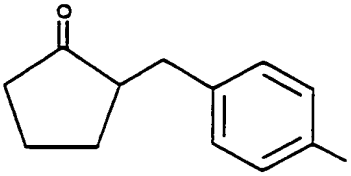


(XXXIII)

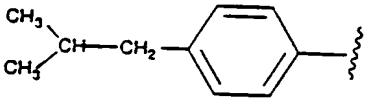
where R is chosen among:



(II)



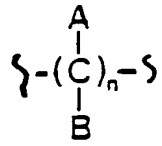
(X)



(III)

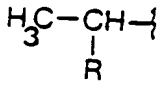
Y is chosen among oxygen, NH, NR_1, where R_1 is a linear or branched alkyl group, and n is comprised between 1 and 10.

2. Nitric esters according to claim 1, characterized in that the fragment:



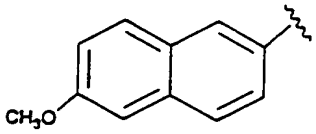
is a linear, branched or cyclic alkylenic group C_2-C_{10}.

3. Derivative of propionic acid according to claim 1, characterized in that M is equal to



(XXXIII)

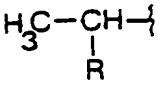
where R is:



(II)

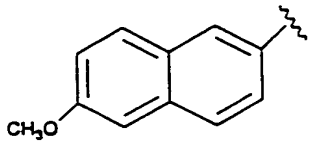
A and B are equal to hydrogen, Y is equal to oxygen, and n is equal to four.

4. Derivative of propionic acid according to claim 1, characterized in that M is equal to



(XXXIII)

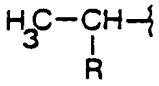
where R is:



(II)

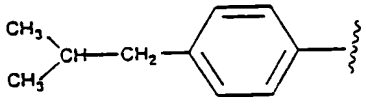
A and B are equal to hydrogen, Y is equal to NH, and n is equal to four.

5. Derivatives of propionic acid according to claim 1, characterized in that M is equal to



(XXXIII)

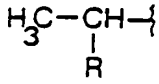
where R is equal to:



(III)

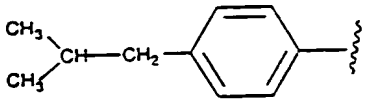
Y is equal to oxygen, A and B are equal to hydrogen, and n is equal to four.

6. Derivative of propionic acid according to claim 1, characterized in that M is equal to



(XXXIII)

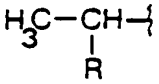
where R is equal to:



(III)

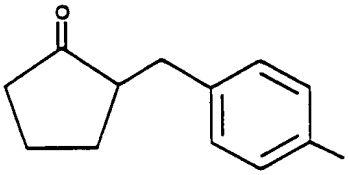
Y is equal to NH, A and B are equal to hydrogen, and n is equal to four.

7. Derivative of propionic acid, according to claim 1, characterized in that M is equal to



(XXXIII)

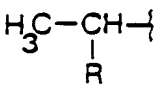
where R is equal to



(X)

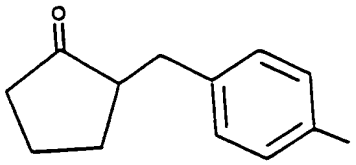
A and B are equal to hydrogen, y is equal to oxygen and n is equal to four.

8. Derivative of propionic acid according to claim 1, characterized in that M is equal to



(XXXIII)

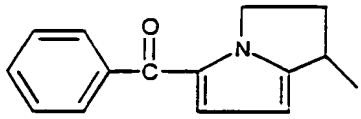
where R is equal to



(X)

A and B are equal to hydrogen, y is equal to NH and n is equal to four.

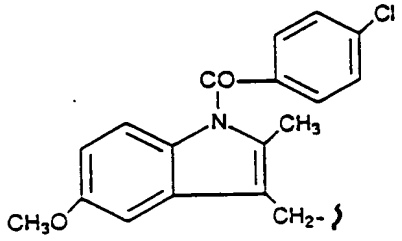
9. Derivatives of 5-benzoyl -1,2-dihydro-3H-pyrrolo[1,2-a] pyrrole -1-carboxylic acid according to claim 1, characterized in that M is equal to



(XXX)

A and B are equal to hydrogen, Y is equal to oxygen and n is equal to four.

10. Derivatives of 1-(p- chlorobenzoyl) -5-methoxy - 2-methyl-3-indolylacetic acid according to claim 1, characterized in that M is equal to



(XXXII)

A and B are equal to hydrogen, Y is equal to oxygen and

n is equal to four.

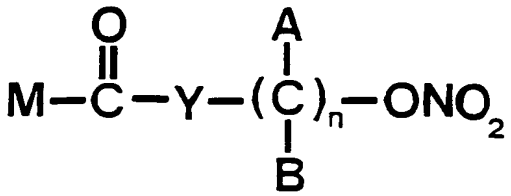
11. Nitric esters according to claim 1, characterized in that they are utilizable in the pharmaceutical field as anti-inflammatory agents.

12. Nitric esters according to claim 1, characterized in that they are utilizable in the pharmaceutical field as analgesic agents.

13. Nitric esters according to claim 1, characterized in that they are utilizable in the treatment of rheumatic illnesses, in the treatment of disorders of an immunologic nature and of the moderate to medium painful states.

14. Nitric esters according to claim 1, characterized in that they are utilizable in the treatment of the diseases of the cardiovascular system, in the treatment of senile dementia, in the treatment of miocardial and brain ischemiae and in cases of arterial thrombosis.

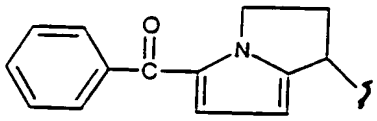
15. Process for the preparation of nitric esters according to claim 1 and having the following general formula:



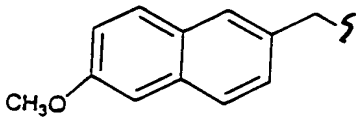
(IA)

where A and B are chosen among hydrogen, linear or branched, substituted or non substituted alkyl chains,

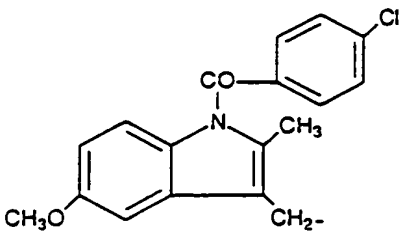
M is chosen among



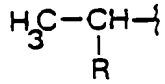
(XXX)



(XXXI)

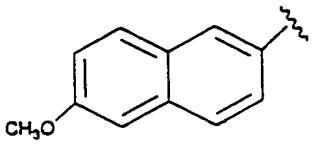


(XXXII)

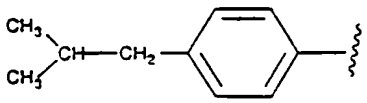


(XXXIII)

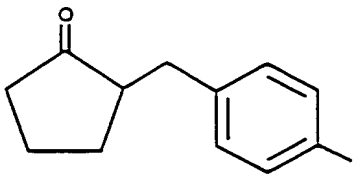
where R is chosen among:



(II)



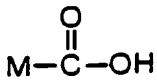
(III)



(X)

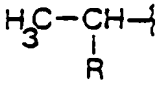
Y is chosen among oxygen, NH, NR_1, where R_1 is a linear or branched alkyl group, and n is comprised between 1 and 10, characterized in that it comprises the following steps:

- Preparation of sodium salt of derivatives having the following general formula:



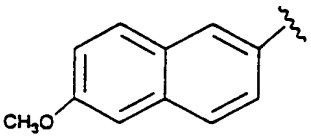
(VIA)

where M is chosen among (XXX), (XXXI), (XXXII),

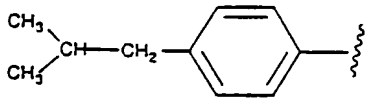


(XXXIII)

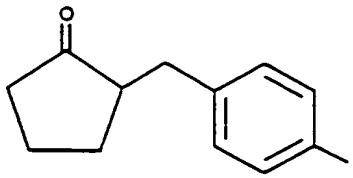
where R is chosen among the following structures:



(II)



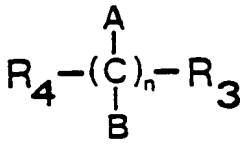
(III)



(X)

or preparation of derivatives (VIA) functionalized to the carboxylic group, such as acylic chlorides, anhydrides or the like;

- Reaction between the sodium salt of said derivatives (VIA) or of said derivatives (VIA) functionalized to the carboxylic group, with a compound having the following general formula:



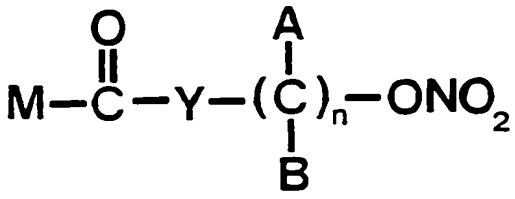
(VII)

where:

R_4 is chosen among chlorine, bromine, NHR_5 with R_5 hydrogen, linear or branched alkyl chain, A and B are chosen among hydrogen, linear or branched, substituted or non substituted alkyl chains, R_3 is chosen among chlorine, bromine and iodine, and n is comprised between 1 and 10, with ensuing production of the relevant monomeric esters or the relevant amides;

- Reaction of said monomeric esters or said amides with a nitrating agent such as $AgNO_3$ or the like, with ensuing production of nitric esters (IA).

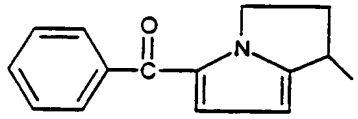
16. Process for the preparation of nitric esters according to claim 1 and having the following general formula:



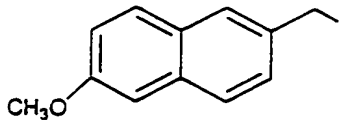
(IA)

where:

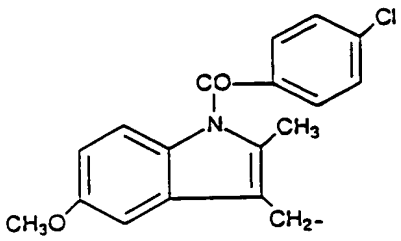
A and B are chosen among hydrogen, linear or branched, substituted or non substitured alkyl chains, M is chosen among



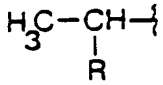
(XXX)



(XXXI)

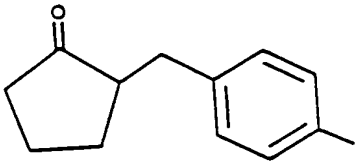


(XXXII)

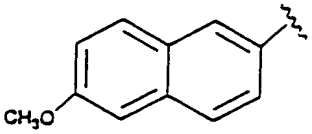


(XXXIII)

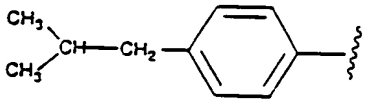
where R is chosen among:



(X)



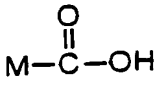
(II)



(III)

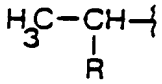
Y is chosen among oxygen, NH, NR_1, where R_1 is a linear or branched alkyl group, and n is comprised between 1 and 10, characterized in that it comprises the following steps:

- Preparation of sodium salt of derivatives having the following general formula:



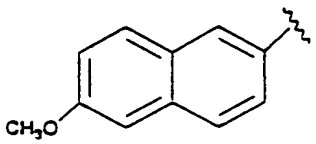
(VIA)

where M is chosen among (XXX), (XXXI), (XXXII),

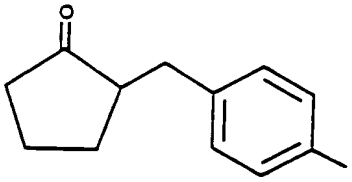


(XXXIII)

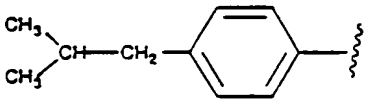
where R is chosen among the following structures:



(II)



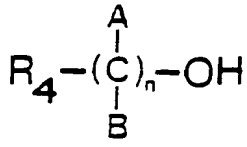
(X)



(III)

or preparation of derivatives (VIA) functionalized to the carboxylic group, such as acylic chorides, anhydrides or the like;

- Reaction between the sodium salt of said derivatives (VIA) or of said derivatives (VIA) functionalized to to the carboxylic group, with a composition having the following generneral formula:



(VIII)

where:

R_4 is chosen en among chlorine, bromine, NHR_5 with R_5 hydrogen, linear or branched alkyl chain, A and B are chosen among hydrogen, linear or branched, substituted or non substituted alkyl chains, and n is comprised between 1 and 10, with ensuing production of the relevant mo monomeric esters or the relevant amides;

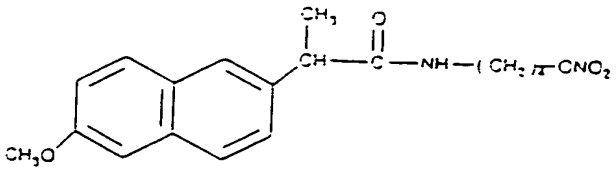
- Reaction of said monomeric esters or said amides with an halogenating compound such as PBr_3 or the like, with ensuing production of said monomeric esters or said amides, characterized by the presence of a terminal halogen group;

- Reaction of said monomeric esters or of said amides, characterized by the presence of a terminal halogen group with a nitrating agent such as $AgNo_3$ or the like, with ensuing production of nitric esters (IA).

17. Pharmaceutical compositions having anti-inflammatory activity characterized in that they comprise at least one nitric ester according to claim 1 as active constituent.

18. Pharmaceutical compositions having analgesic activity characterized in that they comprise at least one nitric ester according to claim 1 as active constituent.

Always according to the processes subject matter of the present invention, also the preparation of a nitric ester derivated from propionic acid proved to be particularly advantageous, having the following formula:



(IV)

which is prepared as described in the following example, that is given hereunder as a mere indication and which does not limit in any way the protection scope of this invention.

EXAMPLE 2

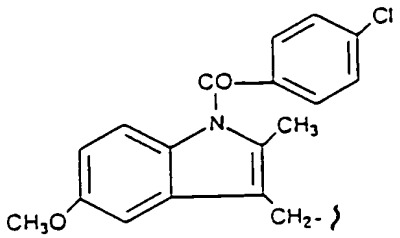
a) 23.9 g of potassium-phtalimide dispersed into 200 ml of anhydrous dimethylformamide were added to a solution of 55.7 g of 1,4-di bromo-butane dissolved in 300 ml of anhydrous dimethylformamide.

The reaction mixture was agitated for 12 hours at room temperature, then diluted with water and extracted with methylene chloride. The methylene chloride was evaporated from the organic phase so obtained at a reduced pressure and then the dimethylformamide was removed by distillation at the pressure of 1.33 KPa (10 mm Hg.)

The residue was regained with water and extracted with methylene chloride.

n is equal to four.

10. Derivatives of 1-(p- chlorobenzoyl) -5-methoxy - 2-methyl-3-indolylacetic acid according to claim 1, characterized in that M is equal to



(XXXII)

A and B are equal to hydrogen, Y is equal to oxygen and n is equal to four.

11. The use of Nitric esters according to claim 1 characterized in that they are utilizable in the pharmaceutical field as anti-inflammatory agents.

12. The use of Nitric esters according to claim 1 characterized in that they are utilizable in the pharmaceutical field as analgesic agents.

13. The use of Nitric esters according to claim 1 characterized in that they are utilizable in the treatment of rheumatic illnesses, in the treatment of disorders of an immunologic nature and of the moderate to medium painful states.

14. The use of Nitric esters according to claim 1 characterized in that they are utilizable in the treatment of the diseases of the cardiovascular system, in the treatment

4 Agent's or applicant's reference number *(if applicable)* PB - 53508

⑤ Claiming an earlier application date

5 Are you claiming that this application be treated as having been filed on the date of filing of an earlier application?

Please mark correct box

Yes ☐ No ☒ ➡ *go to 6*

⬇

please give details below

❑ number of earlier application or patent number

❑ filing date

(day month year)

❑ and the Section of the Patents Act 1977 under which you are claiming:

Please mark correct box

15(4) (Divisional) ☐ 8(3) ☐ 12(6) ☐ 37(4) ☐

⑥ Declaration of priority

⑥ If you are declaring priority from a PCT Application please enter 'PCT' as the country and enter the country code (for example, GB) as part of the application number.

Please give the date in all number format, for example, 31/05/90 for 31 May 1990.

6 If you are declaring priority from previous application(s), please give:

Country of filing	Priority application number *(if known)*	Filing date *(day, month, year)*

The answer must be NO if:
- any applicant is not an inventor
- there is an inventor who is not an applicant, **or**
- any applicant is a corporate body.

Inventorship

7 Are you (the applicant or applicants) the sole inventor or the joint inventors?

Please mark correct box

Yes [ ] No [X] ➡ ***A Statement of Inventorship on Patents Form 7/77 will need to be filed (see Rule 15).***

Please supply duplicates of claim(s), abstract, description and drawing(s).

Checklist

8a Please fill in the number of sheets for each of the following types of document contained in this application.

Continuation sheets for this Patents Form 1/77	-		
Claim(s)	10	Description	23
Abstract	1	Drawing(s)	-

8b Which of the following documents also accompanies the application?

Please mark correct box(es)

Priority documents *(please state how many)*	-
Translation(s) of Priority documents *(please state how many)*	-
Patents Form 7/77 – Statement of Inventorship and Right to Grant *(please state how many)*	-
Patents Form 9/77 – Preliminary Examination/Search	X
Patents Form 10/77 – Request for Substantive Examination	-

You or your appointed agent (see Rule 90 of the Patents Rules 1990) must sign this request.

Request

I/We request the grant of a patent on the basis of this application.

Please sign here ➡

Signed LLOYD WISE, TREGEAR & CO.

Date 6th October 1993 (day month year)

A completed fee sheet should preferably accompany the fee.

Please return the completed form, attachments and duplicates where requested, together with the prescribed fee to:

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OBJECT OF THE INVENTION

The present invention refers to nitric esters of derivatives of propionic acid, their pharmaceutical utilization and the process for their preparation.

PRIOR ART

Some derivatives of propionic acid, such as, for instance, 2-(6-methoxy-2-naphtyl)propionic acid, 2-(4-isobutylphenyl)propionic acid or alpha-Methyl-4-[(2-oxocyclopentyl)methyl]benzeneacetic acid, have been used for a long time in the pharmaceutical field for their anti-inflammatory activity and have been present for many years on the different world markets. The process for the preparation of 2-(6-methoxy-2-naphtyl)propionic acid has been described in the South African Patent N°6707,597, in the German Patent N° 1,934,460, corresponding to the US Patent N°3,637,767 and also in C.A.71,91162j (1969); HARRISON et al. J.Med.Chem. 13,203 (1970); the process for the preparation of 2-(4-isobutylphenyl)propionic acid has been described in Patents GB N°971,700, US N°3,228,831 and US N°3,385,886, and also in T. SHIORI, N. KAWAI, J.Org. Chem. 43,2936 (1978); J.T. PINHEY, B.A. ROWE, Tetrahedron Letters 21, 965 (1980);while the process for the preparation of alpha-methyl-4-[(2-oxocyclopentyl)methyl]benzenacetic acid has been described in the German

Patent N°2,814,556 and in US Patent N°4,161,538.

In the case of 2-(6-methoxy-2-naphtyl)propionic acid, the pharmacological profile is described in ROSZKOWSKI et al. J. Pharmacol. Exp. Ther. 179,114 (1971), while the pharmacological profile of 2-(4-isobutylphenyl)propionic acid is reported in ADAMS et al. Arch. Pharmacodyn. Ther. 178,115 (1969).

The utilization of these derivatives of propionic acid as anti-inflammatory agents involves, as known, extremely severe adverse reactions affecting, for instance, the gastrointestinal system, as well as damages to liver and kidneys. There are many experimental evidences [S. MONCADA, R.M.J. PALMER, E.A. HIGGS, Pharmacological Reviews, 43 (2), 109-142 (1991); T.F. LUSHER, C.M. BOULANGER, Y. DOHI, Z. YANG, Hypertension, 19,117-130 (1992)], on which basis the integrity of vasal endothelium is assumed to constitute a basic protection barrier against the onset of pathological processes in different organs and systems.

Such protection barrier, and therefore the integrity of vasal endothelium, is ensured on the physiological plane, by the presence of nitric oxide and prostacyclin.

The treatment with non steroidal drugs having an anti-inflammatory activity, such as, for instance, 2-(6-

methoxy-2-naphtyl)propionic acid or 2-(4-isobutylphe-

l)propionic acid, causes the inhibition of cyclo-oxygenase, an enzyme which synthesizes the precursor of prostacyclin.

As a consequence, the production of prostacyclin being so inhibited, the tissue reserve of same is markedly depauperated and therefore the integrity of vasal endothelium is compromised.

As said, because of this endothelial damage due to the reduction of prostacyclin, diffuse pathological processes break out which affect the gastrointestinal system, the renal system and the liver.

Furthermore, as known, during inflammatory processes, new enzyme proteins, such as for example, nitric oxide synthetase, are induced; these enzyme proteins are partially responsible for the supporting of the inflammation [T.I.P.S. 14,287(1993)].

OBJECTS OF THE INVENTION

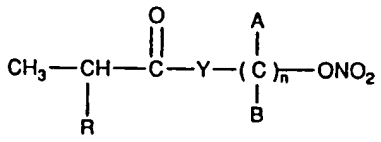
Object of the present invention is that of providing a product which, while assuring at least the maintenance of the pharmacological activity which is characteristic of the known anti-inflammatory agents, is capable of eliminating the adverse reactions brought about by the treatment with said agents.

Another object of the present invention is that of

realizing a process for the preparation of derivatives of propionic acid having an anti-inflammatory activity and exempt from the adverse reactions that are typical of anti-inflammatory agents.

DESCRIPTION OF THE INVENTION

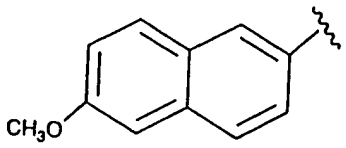
These and still further objects and associated advantages which shall clearly result from the following description, are reached by derivatives of propionic acid which, according to the present invention, have the following general formula:



(I)

where:

A and B are chosen among hydrogen, linear or branched, substituted or non substituted alkyl chains, while R is chosen among:



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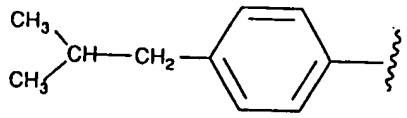
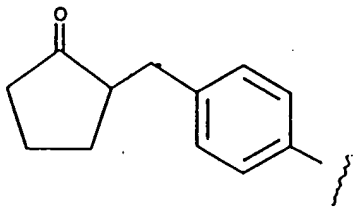


(III)



(X)

is chosen among oxygen, NH, NR_1, where R_1 is a linear or branched alkyl group, and n is comprised between 1 and 10.

In fact, it has been observed that the introduction of a group such as a terminal nitric ester in the derivatives of propionic acid as in (I) permits to mantain the pharmacological activity which is characteristic of anti-inflammatory non steroidal agents, while eliminating the adverse reactions caused by the treatment with such drugs. Furthermore, the introduction of a terminal nitric ester in the derivatives of propionic acid as in (I), permits to potentiate the anti-inflammatory effect compared with the well known non-steroidal anti-inflammatory drugs; such increase is made by the terminal nitric ester group, which can be considered as a source of nitric oxide and which can exert additional anti-inflammatory effects.

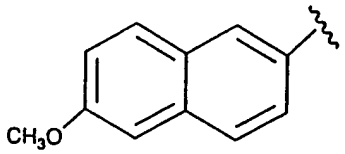
It has been also observed that the derivatives (I) are useful in the treatment of different unhealthy conditions, such as, for instance, rheumatic diseases in general, disorders of an immunologic nature, and they can also alleviate moderate-medium painful states of any kind.

Moreover, the derivatives (I) subject matter of this

invention, are useful in the treatment of the illnesses of the cardiovascular system, and in particular in the treatment of myocardial and brain ischemiae, as well as in some cases of arterial thrombosis.

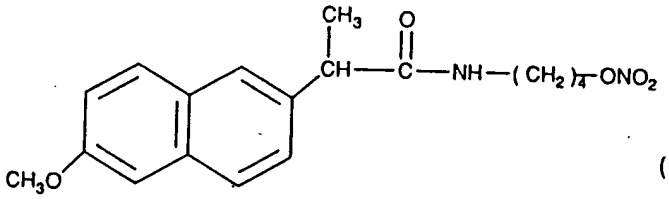
Always according to this invention, a nitric ester of a derivative of propionic acid (I) proved to be particularly advantageous, where:

hydrogen is chosen as A and B, as R is chosen:



(II)

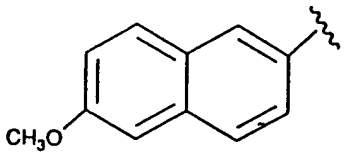
NH is chosen as Y, and n is equal to four, according to the following formula:



(IV)

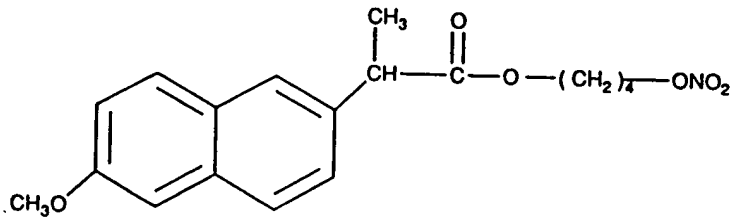
A nitric ester of a derivative of propionic acid (I) has also proved to be particularly advantageous according to this invention, where:

hydrogen is chosen as A and B, as R is chosen:



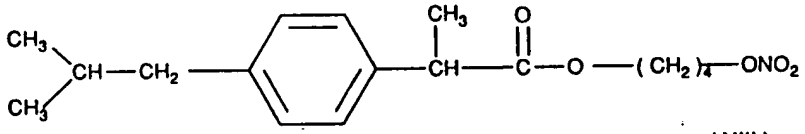
(II)

oxygen is chosen as Y, an n is equal to four, according to the following formula:



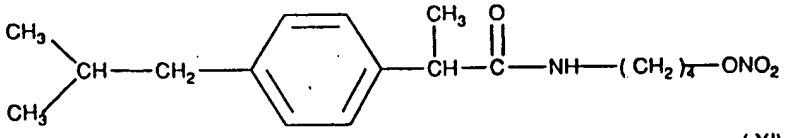
(V)

Also the nitric esters of derivatives of 2-(4-isobutylphenyl)propionic acid have proved to be particularly advantageous according to this invention, having the following formulae:



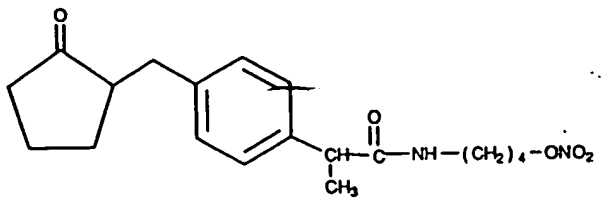
(XIII)

and

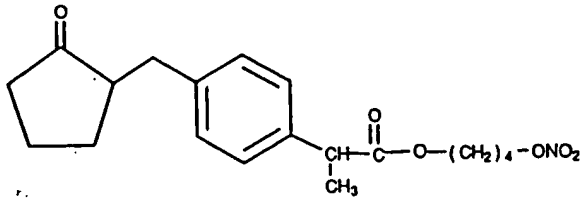


(XIV)

Always according to the present invention, nitric esters of derivatives of propionic acid (I) have proved to be particularly advantageous, having the following formulae:



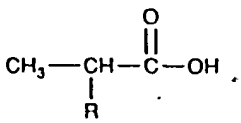
(XI)



(XII)

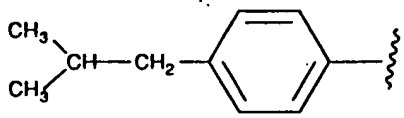
For the preparation of nitric esters of derivatives (I) of propionic acid subject matter of the present invention, a first process has proved to be particularly advantageous which, according to the present invention, includes the following steps:

- Preparation of sodium salt of derivatives of propionic acid having the following general formula:

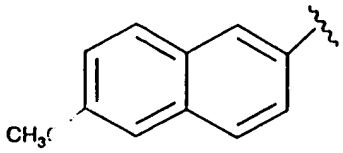


(VI)

where R is chosen among the following structures:

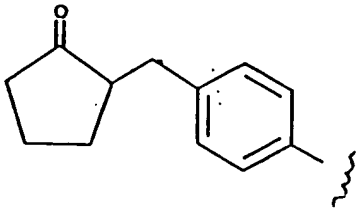


(III)



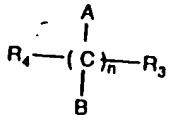
(II)

(X)



or preparation of derivatives (VI) of propionic acid functionalized to the carboxylic group as acylic chlorides, anhydrides or the like;

- Reaction between the sodium salt of said derivatives (VI) of propionic acid or of said derivatives (VI) of propionic acid functionalized to the carboxylic group, with a composition having the following general formula:



(VII)

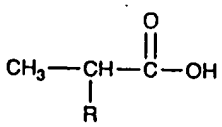
where:

R_4 is chosen among chlorine, bromine, NHR with R hydrogen, linear or branched alkyl chain, A and B are chosen among hydrogen, linear or branched, substituted or non substitutes alkyl chains, R_3 is chosen among chlorine, bromine and iodine, and n is comprised between 1 and 10, with ensuing production of the relevant monomeric esters or the relevant amides;

- Reaction of said monomeric esters or said amides with a nitrating agent such as $AgNO_3$ or the like, with ensuing production of nitric esters of derivatives of propionic acid (I).

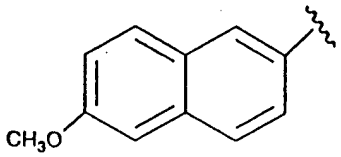
A second process has also proved to be particularly advantageous which, always according to the present invention, includes the following steps:

- Preparation of sodium salt of derivatives of propionic acid having the following general formula:

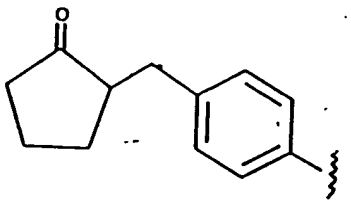


(VI)

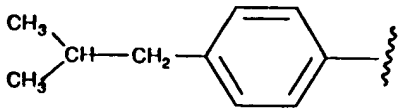
where R is chosen among the following structures:



(II)



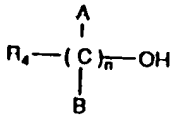
(X)



(III)

or preparation of derivatives (VI) of propionic acid functionalized to the carboxylic group, such as acylic chlorides, anhydrides or the like;

- Reaction between the sodium salt of said derivatives (VI) of propionic acid or of said derivatives (VI) of propionic acid functionalized to the carboxylic group, with a composition having the following general formula:



(VIII)

where;

R_4 is chosen among chlorine, bromine, NHR with R hydrogen, linear or branched alkyl chains, A and B are

chosen among hydrogen, linear or branched, substituted or non substituted alkyl chains, and n is comprised between 1 and 10, with ensuing production of the relevant monomeric esters or the relevant amides;

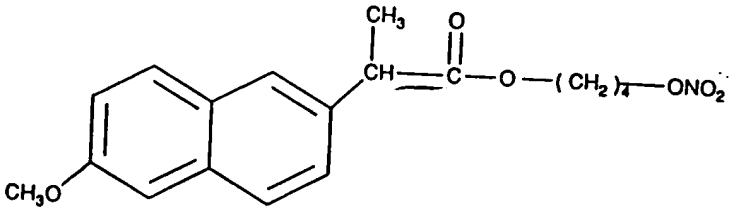
- Reaction of said monomeric esters or said amides with an halogenating composition such as PBr_3 or the like, with ensuing prouction of said monomeric esters or said amides characterized by the presence of a terminal halogen group;

- Reaction of said monomeric esters or said amides characterized by the presence of a terminal halogen group, with a nitrating agent such as $AgNO_3$ or the like, with ensuing production of nitric esters of derivatives of propionic acid (I).

The solvents which are utilized in the processes subject matter of the present invention are preferably chosen among chloroform, methylene chloride, acetonitrile, dimethylformamide, tetrahydrofuran, 1,4-dioxane and the like.

Such processes for the preparation of derivatives of propionic acid (I), subject matter of the present invention, consist of a limited number of steps, which permits to obtain in a short time the products which derive from these processes, with satisfactory yields and in high amounts, also on the industrial level.

cording to the processes subject matter of this invention, the preparation of a nitric ester derived from propionic acid has proved to be particularly advantageous, having the following formula:



(V)

which is prepared as described in the example that is given hereunder as a mere indication and which does not limit in any way the protection scope of the invention.

EXAMPLE 1

a) 0.59 g of EtONa dissolved in 10 ml of ethyl alcohol were added, by slow dripping, to a solution of 2 g of 2-(6-methoxy-2-naphtyl)propionic acid, dissolved in 20 ml of ethyl alcohol. The reaction mixture was stirred for 5 minutes at room temperature, then the solvent was evaporated at a reduced pressure, obtaining 2.1 g of sodium salt of 2-(6-methoxy-2-naphtyl)propionic acid.

The 2.1 g of sodium salt of 2-(6-methoxy-2-naphtyl) propionic acid so obtained were disperded in 40 ml of dimethylformamide and 1.5 g of 1-Br-4-Cl-butane dissol-

ved in 30 ml of dimethylformamide were added by dripping to this dispersion. The reaction mixture was stirred for 12 hours at room temperature, then diluted with water and extracted with methylene chloride. The organic phase so extracted was anhydrified on sodium sulfate and the solvent was evaporated at a reduced pressure until a dry residue of 2 g was obtained.

The residue was purified by chromatography on silica gel, utilizing an eluting mixture constituted by hexane/ether 7/3 (v/v).

The head fractions were collected, the solvent was evaporated at a reduced pressure and 1 g of 2-(6-methoxy-2-naphtyl)propionate of 4-chlorobutyl (IX) was obtained.

IR(cm^{-1}):C=0,1669.

^{1}H-NMR(300MHz) ($CDCl_3$): 1.6ppm (d,3H); 1.75ppm (m, 4H); 3.45ppm (m, 2H); 3.88ppm (q,1H); 3.91ppm (1,3H); 4.1ppm (m, 2H); 7.1-7-7.7ppm (m, aromatics).

Mass spectrometry (i.e.): $M^{+\cdot}$ 320.

b) 0.79 g of $AgNO_3$ dissolved in 1.3 ml of acetonitrile were dripped to 1 g of (IX) obtained as described in a), dissolved in 4,5 ml of acetonitrile. The reaction mixture was stirred for 12 hours at a temperature of 85°C and then filtered.

From the resulting solution, the solvent was evaporated

at a reduced pressure, and a residue was obtained to

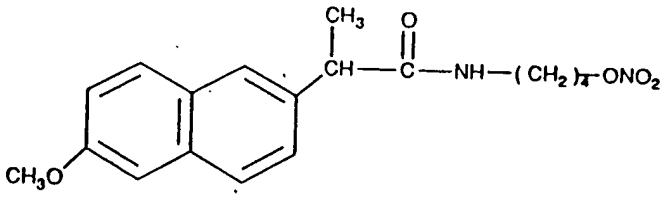
ich 10 ml of methylene chloride were added. The mix so obtained was filtered once again, the organic phase was washed with water and then anhydrified on sodium sulfate. The solvent was evaporated under reduced pressure and 1.8 g of a dry residue was obtained, which was purified by chromatography on silica gel, utilizing an eluting mixture constituted by hexane/ether 7/3 (v/v). The fractions containing the product were collected, the solvent was evaporated at a reduced pressure and 1.5 g of nitric ester of 2-(6-methoxy-2-naphtyl)propionate of 4-hydroxy-butyl (V) were obtained.

IR(cm^{-1}): C=0,1733; ONO_2, 1637.

^{1}H-NMR(300MHz) ($CDCL_3$): 1.6ppm (d,3H); 1.65ppm (m, 4H); 3.8ppm (q, 1H); 3.9ppm (s,3H); 4.1ppm (m, 2H); 4.3ppm (m, 2H); 7.1-7.7ppm (m, aromatics).

Mass spectometry (i.e.) $M^+ \cdot 347$.

Always according to the processes subject matter of the present invention, also the preparation of a nitric ester derivated from propionic acid proved to be particularly advantageous, having the following formula:



(IV)

which is prepared as described in the following example, that is given hereunder as a mere indication and which does not limit in any way the protection scope of this invention.

EXAMPLE 2

a) 23.9 g of potassium-phtalimide dispersed into 200 ml of anhydrous dimethylformamide were added to a solution of 55.7 g of 1,4-di bromo-butane dissolved in 300 ml of anhydrous dimethylformamide.

The reaction mixture was agitated for 12 hours at room temperature, then diluted with water and extracted with methylene chloride. The methylene chloride was evaporated from the organic phase so obtained at a reduced pressure and then the dimethylformamide was removed by distillation at the pressure of 10 mm Hg.

The residue was regained with water and extracted with methylene chloride.

Tha organic phase so obtained was anhydrified and the solvent was evaporated at a reduced pressure until 14.8 g of 1-phtalimide-4-bromo-butane were obtained, which were treated with isopropyl ether and then essiccated.

m.p. = 77°C

b) 32 ml of hydriodic acid were cautiously added to 8.25 g of 1-phtalimido-4-bromo-butane; the mixture was then submitted to heating and kept in ebullition for 24

hours.

ter cooling, the mixture was diluted with water and after filtration the solvent was evaporated at a reduced pressure, obtaining a residue which, once crystallized by ethyl ether, produced 6 g of 4-iodine-butylammonium iodide.

m.p. = 103°C

c) 7 ml of thionyl chloride were cautiously added to a solution of 2.3 g of 2-(6-methoxy-2-naphtyl)propionic acid in 15 ml of anhydrous chloroform. The reaction mixture was stirred for 40 minutes at room temperature and then the solvent was evaporated at a reduced pressure, obtaining 2.23 g of 2-(6-methoxy-2-naphtyl)propionylchloride.

2.3 g od 2-(6-methoxy-2-naphtyl)propionylchloride were dissolved in pyridine and the solution was cooled at the temperature of 0°C.

3.27 g of 4-iodobutylammonium iodide were added to this solution and the ixture so obtained was agitated for 1 hour at 0°C and then diluted with water and extracted with methylene chloride.

The organic phase so obtained was washed initially with a 10% solution of hydrochloric acid and afterward with a saturated solution of sodium bicarbonate, then the solvent was evaporated at a reduced pressure, obtaining

3.2 g of a dry residue. The residue was purified by chromatography on silica gel, utilizing methylene chloride as eluent.

The intermediate fractions were collected, the solvent was evaporated at a reduced pressure and 1.6 g of 2-(6-methoxy-2-naphtyl)-4-iodobutyl propionamide (XX) were obtained.

IR (cm^{-1}): NH, 3294; C=0,1651.

^{1}H-NMR(300MHz) ($CDCl_3$): 1.1-1.75 ppm (m, 4H); 1.6ppm (d, 3H); 3.1ppm (t, 2H); 3.2ppm (q, 2H); 3.7ppm (q, 1H); 3.9ppm (s, 3H); 5.35ppm (m, NH); 7.1-7.75ppm (m, aromatics).

d) A suspension of 1.6 g of 2-(6-methoxy-2-naphtyl)-4-iodobutyl propionamide in 20 ml of acetonitrile was heated at a temperature of about 40°C and stirred until a solution was obtained to which 1.0 g of $AgNO_3$ were added.

The mixture was stirred for 1 hour at room temperature, then filtered and the solvent was evaporated at a reduced pressure. The residue obtained was regained with methylene choride, the resulting mixture was filtered and the solvent was evaporated at a reduced pressure, and 0,8 g of dry residue were obtained which were purified by chromatography on silica gel, utilizing an eluting mixture constituted by methylene chlo-

ride/ethyl acetate 9/1 (v/v).

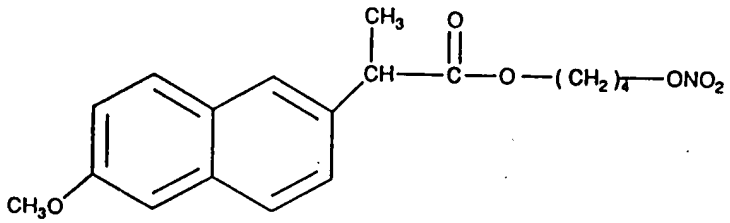
e head fractions were collected, the solvent was evaporated at a reduced pressure and 0.75 g of nitric ester of 2-(6-methoxy-2-naphtyl)-4-hydroxybutyl propionamide (IV) were obtained.

IR(cm^{-1}): C=0,1672; NH, 3294; ONO_2, 1637

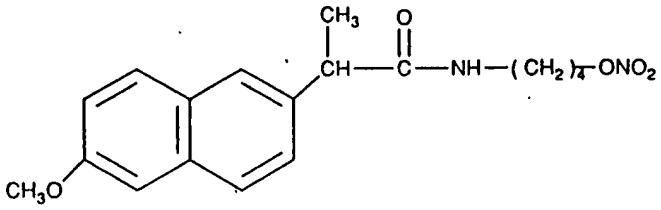
Mass spectometry (i.e.) M^{+}·346.

^{1}H-NMR(80mhz) ($CDCl_3$): 1.3ppm-1.6ppm (m, 4H); 1.7ppm (d, 3H); 3.1ppm (q, 2H); 3.7ppm (q, 1H); 3.9ppm (s, 3H); 4.3ppm (m, 2H); 5.6ppm (m, NH); 7.05-7.8ppm (m, aromatics).

Through biological assays the anti-inflammatory and analgesic activity were determined, for instance of nitric esters of derivatives of propionic acid (I) having the following formulae:



(V)



(IV)

The anti-inflammatory activity of said nitric esters of derivatives of propionic acid was determined in Wistar rats utilizing the method of carrageenan edema, as reported in C.A. WINTER, E. RISLEY, G.W. NUSS, Proc. Soc. Exp. Biol. Med. 111,544-547 (1962), while the analgesic activity of said derivatives was determined in Swiss mice as reported by L.C. HENDERSHOT, J. FORSAITH, J.Pharmacol. Exp. Ter. 125,237-249 (1959).

The anti-inflammatory and analgesic activity of said derivatives resulted to be comparable to 2-(6-methoxy-2-naphtyl)propionic acid taken as a reference.

Then, the acute toxicity of said derivatives (IV) and (V) was evaluated by oral administration of a single dose of each composition (IV) and (V), utilizing groups of 10 Swiss mice for each derivative.

The incidence of lethality and the onset of a toxic symptomatology were reported for an observation period of 14 days.

Even after the administration of a dose of 750 mg/kg of composition (IV) or composition (V) no apparent toxicity simptoms were observed in the treated animals.

Further biological assays were carried out in order to define the pharmaco-toxicological profile of the stu-

died compounds, in particular of composition (V), pared with 2-(6-methoxy-2-naphtyl)propionic acid taken as reference.

A. PHARMACODYNAMIC ACTIVITY

ACUTE MODELS

Rat carrageenan paw edema. On the basis of preliminary experiments, the compound (V) and 2-(6-methoxy-2-naphtyl)propionic acid prove to have a comparable efficacy; the effective dose is comprised in the range from 1 to 10 mg/kg p.o.

SUBACUTE MODELS

Rat adjuvant arthritis. The animals treated for 19 running days (from the 3rd to the 20th day after the inducing injection) with composition (V) or with 2-(6-methoxy-2-naphtyl)propionic acid, both of them at doses of 3 mg/kg p.o., showed a significant and comparable reduction in arthritic symptomatology compared with controls.

B. GASTROINTESTINAL TOLERABILITY

Damage to the gastric mucosa of the rat. The compound (V) was studied in comparison with 2-(6-methoxy-2-naphtyl)propionic acid taken as reference, both of them at doses comprised between 3 and 30 mg/kg p.o.; the compound (V) proved to be significantly better tolerated than 2-(6-methoxy-2-naphtyl)propionic acid. 2-(6-

methoxy-2-naphtyl)propionic acid already at 3 mg/kg caused gastric damages, and such effects resulted to be dose-dependent, while the compound (V) proved to be well tolerated even at doses of 30 mg/kg.

C. GENERAL PHARMACOLOGY

A secondary pharmacological evaluation of compound (V) was carried out in comparison with 2-(6-methoxy-2-naphtyl)propionic acid. No considerable additional effects with respect to the primary pharmacological activity were observed on central nervous system, on the autonomous system, on the cardiovascular, respiratory and gastrointestinal systems.

D. TOXICOLOGY

Acute toxicity in rodents. Preliminary studies were carried out in rodents, utilizing two administration routes. No simptoms of apparent toxicity were observed in animals treated with oral or intraperitoneal doses of 300 mg/kg.

Maximum tolerated dose in non-rodents. Preliminary studies have indicated that compound (V) was very well tolerated in the dog, an animal species which is known to be particularly sensitive to the ulcerogenic activity of anti-inflammatory agents in general. The animals received increasing oral doses of compound (V) up to 30 mg/kg and no apparent symptoms were observed. In compa-

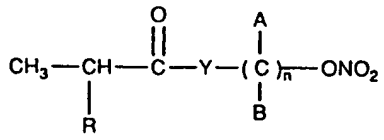
rison, 2-(6-methoxy-2-naphtyl)propionic acid, adminis-

:red at doses of 10 mg/kg, caused the death of the

animals.

CLAIMS

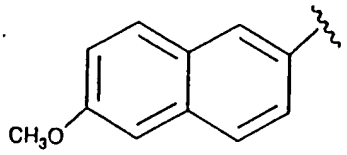
1. Derivatives of propionic acid characterized in that they have the following general formula:



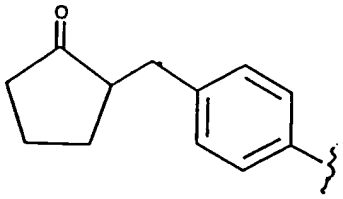
(I)

where:

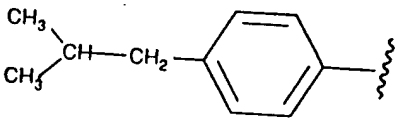
A and B are chosen among hydrogen, linear or branched, substituted or non substituted alkyl chains, R is chosen among:



(II)



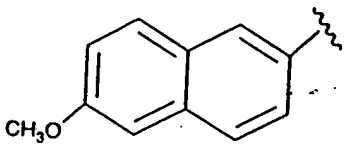
(X)



(III)

Y is chosen among oxygen, NH, NR_1, where R_1 is a linear or branched alkyl group, and n is comprised between 1 and 10.

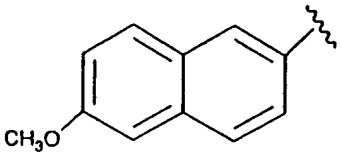
Derivative of propionic acid according to claim 1, characterized in that R is:



(II)

A and B are equal to hydrogen, Y is equal to oxygen, and n is equal to four.

3. Derivative of propionic acid according to claim 1, characterized in that R is:

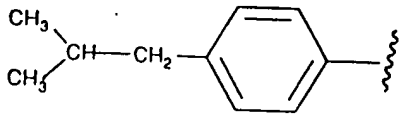


(II)

A and B are equal to hydrogen, Y is equal to NH, and n is equal to four.

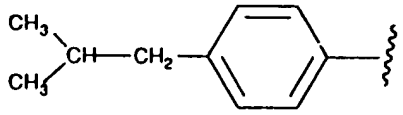
4. Derivatives of propionic acid according to claim 1, characterized in that R is equal to:

(III)



Y is equal to oxygen, A and B are equal to hydrogen, and n is equal to four.

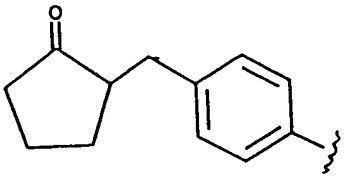
5. Derivative of propionic acid according to claim 1, characterized in that R is equal to:



(III)

Y is equal to NH, A and B are equal to hydrogen, and n is equal to four.

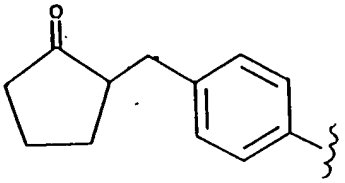
6. Derivative of propionic acid, according to claim 1, characterized in that R is equal to



(X)

A and B are equal to hydrogen, y is equal to oxygen and n is equal to four.

7. Derivative of propionic acid according to claim 1, characterized in that R is equal to



(X)

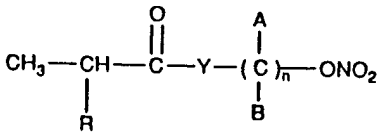
and B are equal to hydrogen, y is equal to NH and n is equal to four.

8. Derivatives of propionic acid according to claim 1, characterized in that they are utilizable in the pharmaceutical field as anti-inflammatory agents.

9. Derivatives of propionic acid according to claim 1, characterized in that they are utilizable in the treatment of rheumatic illnesses, in the treatment of disorders of an immunologic nature and of the moderate to medium painful states.

10. Derivatives of propionic acid according to claim 1, characterized in that they are utilizable in the treatment of the diseases of the cardiovascular system, in the treatment of miocardial and brain ischemiae and in cases of arterial thrombosis.

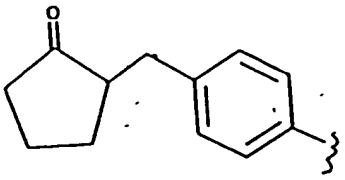
11. Process for the preparation of derivatives of propionic acid according to claim 1 and having the following general formula:



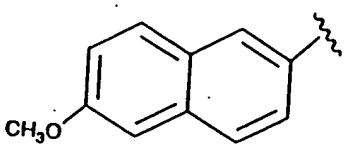
(I)

where A and B are chosen among hydrogen, linear or branched, substituted or non substituted alkyl chains,

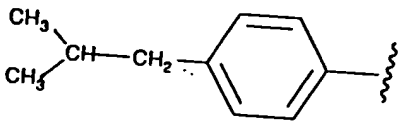
R is chosen among:



(X)



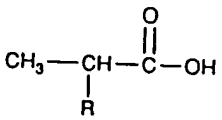
(II)



(III)

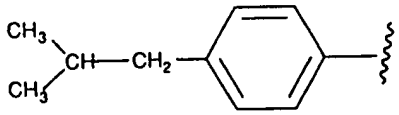
Y is chosen among oxygen, NH, NR_1, where R_1 is a linear or branched alkyl group, and n is comprised between 1 and 10, characterized in that it comprises the following steps:

- Preparation of sodium salt of derivatives of propionic acid having the following general formula:

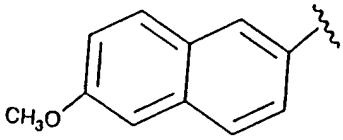


(VI)

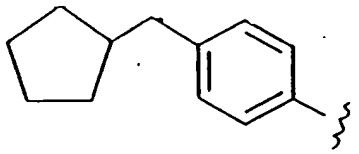
where R is chosen among the following structures:



(III)



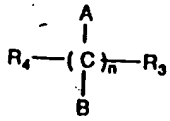
(II)



(X)

or preparation of derivatives (VI) of propionic acid functionalized to the carboxylic group, such as acylic chlorides, anhydrides or the like;

- Reaction between the sodium salt of said derivatives (VI) of propionic acid or of said derivatives (VI) of propionic acid functionalized to the carboxylic group, with a compound having the following general formula:



(VII)

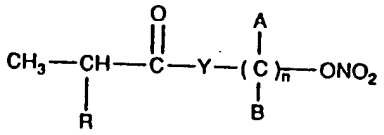
where:

R_4 is chosen among chlorine, bromine, NHR with R hydrogen, linear or branched alkyd chain, A and B are chosen among hydrogen, linear or branched, substituted or non substituted alkyl chains, R_3 is chosen among chlorine, bromine and iodine, and n is comprised between 1 and 10, with ensuing production of the relevant monomeric esters or the relevant amides;

- Reaction of said monomeric esters or said amides with a nitrating agent such as $AgNO_3$ or the like, with

ensuing production of nitric esters of derivatives of propionc acid (I).

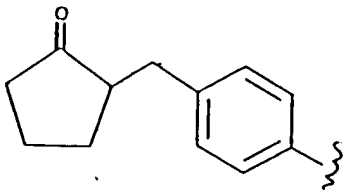
12. Process for the preparation of derivatives of propionic acid according to claim 1 and having the following general formula:



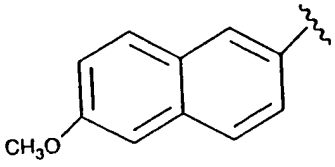
(I)

where:

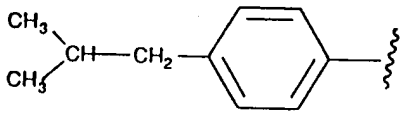
A and B are chosen among hydrogen, linear or branched, substituted or non substitured alkyl chains, R is chosen among:



(x)



(II)



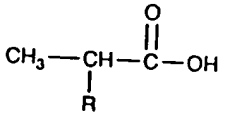
(III)

Y is chosen among oxygen, NH, NR_1, where R_1 is a linear or branched alkyl group, and n is comprised between 1

and 10, characterized in that it comprises the follo-

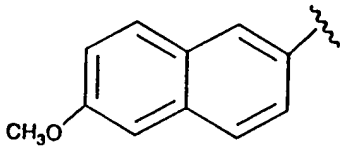
ɟ steps:

- Preparation of sodium salt of derivatives of propionic acid having the following general formula:

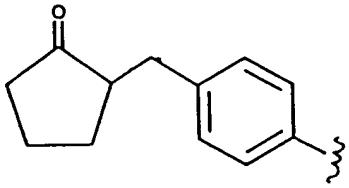


(VI)

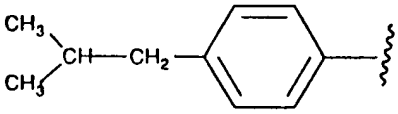
where R is chosen among the following structures:



(II)



(X)

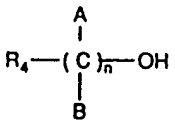


(III)

or preparation of derivatives (VI) of propionic acid functionalized to the carboxylic group, such as acylic chorides, anhydrides or the like;

- Reaction between the sodium salt of said derivatives (VI) of propionic acid or of said derivatives (VI) of

propionic acid functionalized to the carboxylic group, with a composition having the following general formula:



(VIII)

where:

R_4 is chosen among chlorine, bromine, NHR with R hydrogen, linear or branched alkyl chain, A and B are chosen among hydrogen, linear or branched, substituted or non substituted alkyl chains, and n is comprised between 1 and 10, with ensuing production of the relevant monomeric esters or the relevant amides;

- Reaction of said monomeric esters or said amides with an halogenating compound such as PBr_3 or the like, with ensuing production of said monomeric esters or said amides, characterized by the presence of a terminal halogen group;

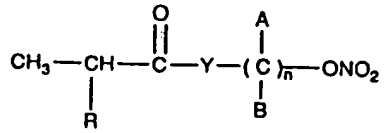
- Reaction of said monomeric esters or of said amides, characterized by the presence of a terminal halogen group with a nitrating agent such as $AgNo_3$ or the like, with ensuing production of nitric esters of derivatives of propionic acid (I).

13. A derivative of propionic acid as claimed in Claim 1 substantially as herein described with reference to the Example.

14. A process as claimed in Claim 11 substantially as herein described with reference to the Example.

NITRIC ESTERS OF DERIVATIVES OF PROPIONIC ACID AND PROCESS FOR THEIR PREPARATION.

The present invention refers to nitric esters of derivatives of propionic acid having the following general formula:



(I)

their pharmaceutical use and the process for their preparation.